DRUG ABSORPTION AND BIOAVAILABILITY

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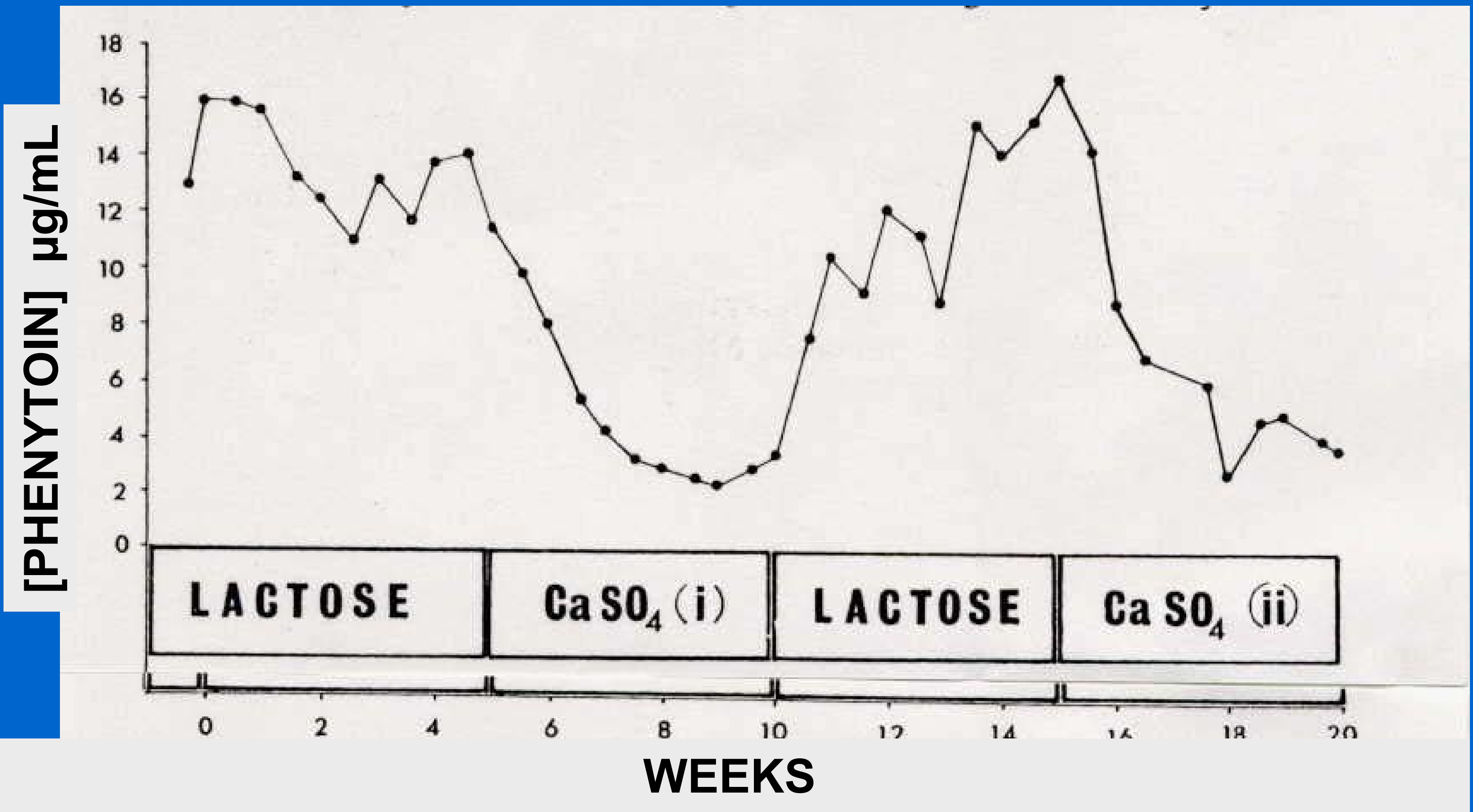
GOALS OF DRUG ABSORPTION AND BIOAVAILABILITY LECTURE

- FACTORS AFFECTING DRUG ABSORPTION
- ESTIMATION OF BIOAVAILABILITY
- CLINICAL SIGNIFICANCE OF DIFFERENCES IN BIOAVAILABILITY
- PREDICTION OF BIOAVAILABILITY AS PART OF HIGH-THROUGHPUT DRUG CANDIDATE SCREENING

FACTORS AFFECTING DRUG ABSORPTION

- BIOPHARMACEUTIC FACTORS
  - TABLET COMPRESSION
  - COATINGS AND MATRIX
  - EXCIPIENTS
- INTERACTIONS
  - FOOD
  - OTHER DRUGS
  - BACTERIA
- PHYSIOLOGICAL FACTORS

CHANGE IN PHENYTOIN EXCIPIENTS RESULTS IN EPIDEMIC TOXICITY*



* Bochner F, et al. Proc Aust Assoc Neurol 1973;9:165-70

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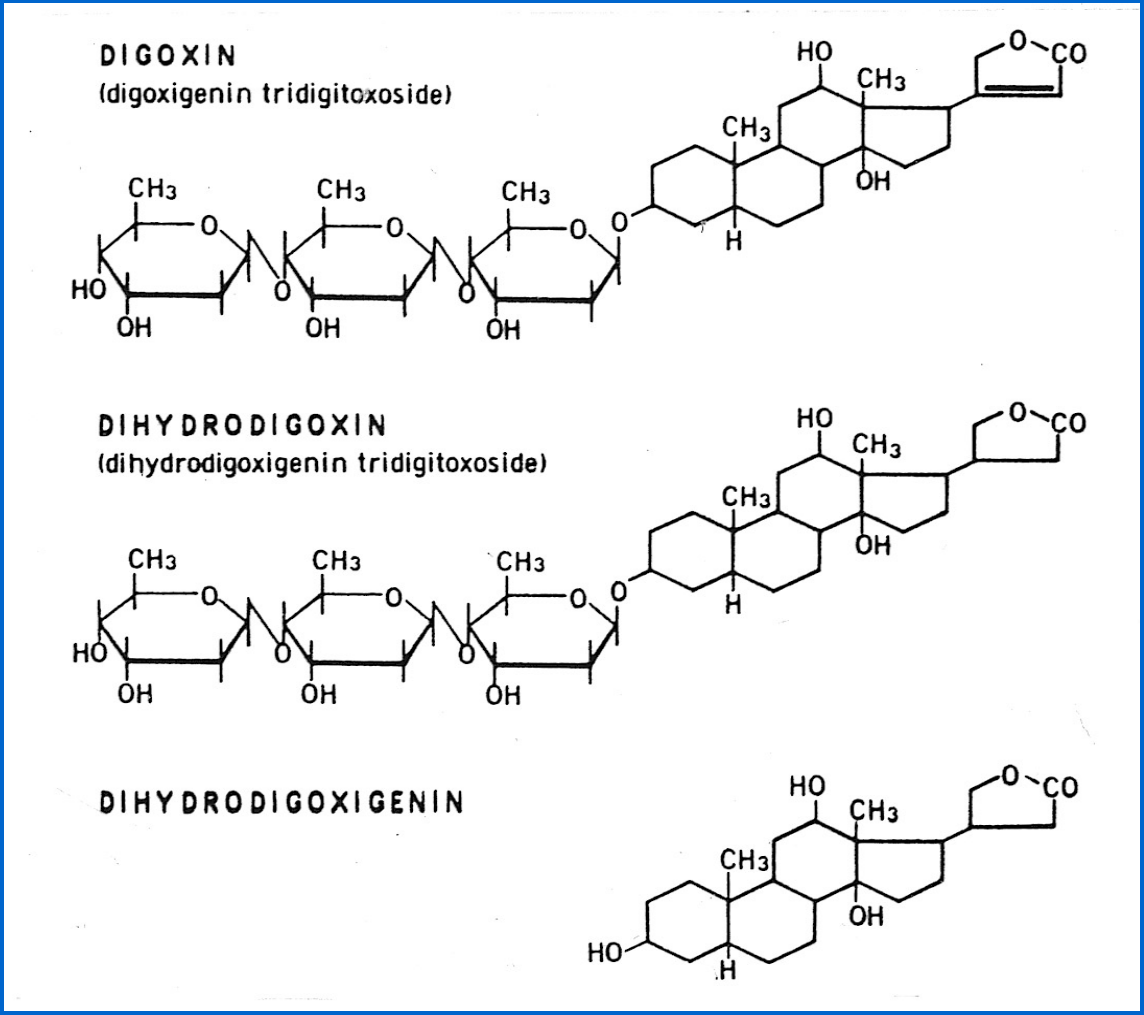
ENTERIC METABOLISM OF DIGOXIN



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MECHANISMS OF DRUG ABSORPTION

- **PASSIVE NON-IONIC DIFFUSION**
  - **PRIMARY MECHANISM**

- **SPECIALIZED TRANSPORT MECHANISMS**
  - **LARGE NEUTRAL AMINO ACID TRANSPORTER** ***(L-DOPA, α-METHYLDOPA, BACLOFEN)***
  - **OLIGOPEPTIDE TRANSPORTER** ***(AMINO-β-LACTAMS, ACE INHIBITORS)***
  - **MONOCARBOXILIC ACID TRANSPORTER** ***(SALICYLIC ACID, PRAVASTATIN)***

FALLACIES CONCERNING GASTRIC ABSORPTION OF DRUGS

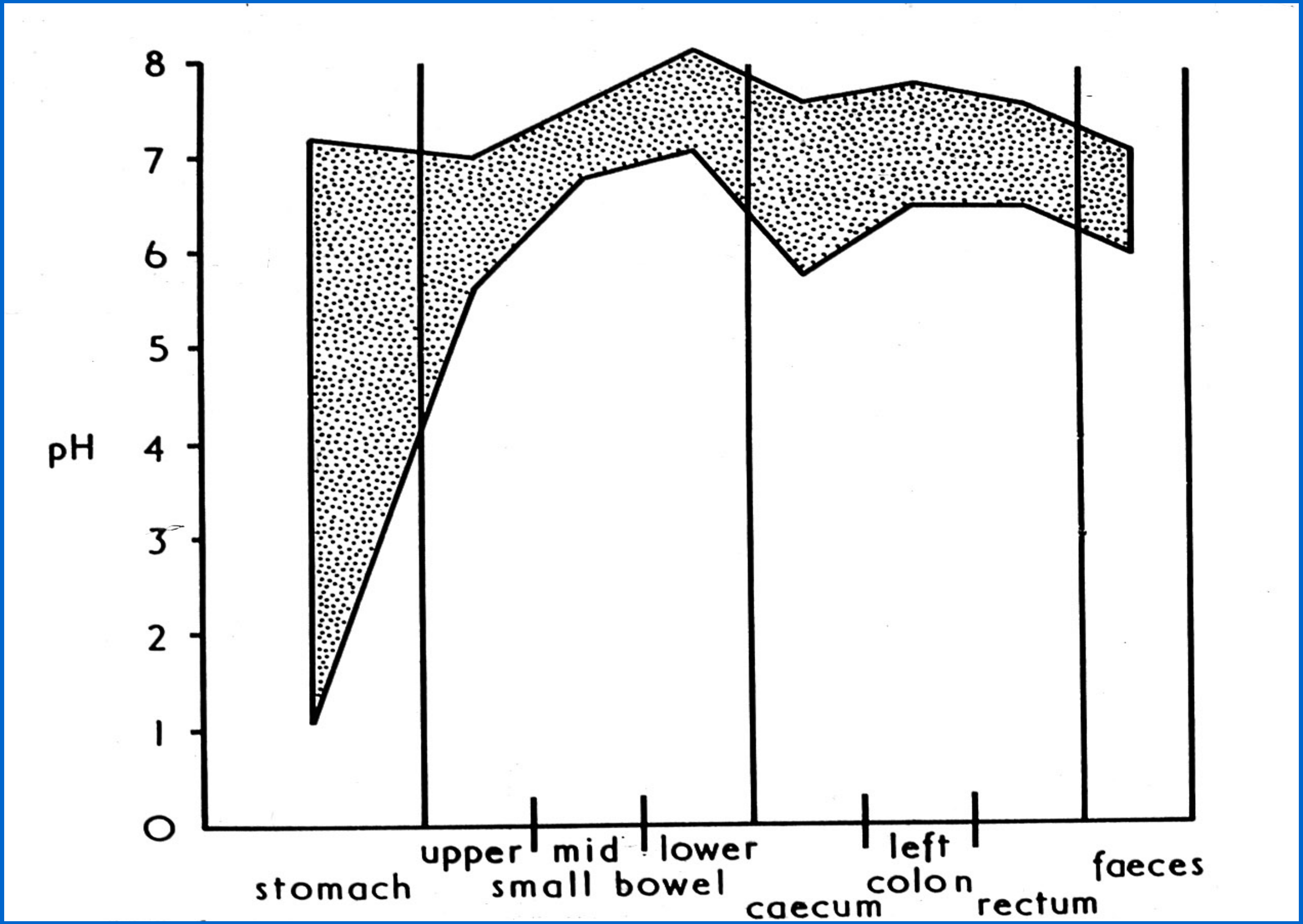
- ACIDIC DRUGS ARE ABSORBED IN THE STOMACH, BASIC DRUGS ARE ABSORBED IN THE SMALL INTESTINE
- GASTRIC pH IS ALWAYS ACIDIC

ASPIRIN ABSORPTION FROM STOMACH AND SMALL INTESTINE*

TABLE 1: ASPIRIN (ASA) ABSORPTION FROM SIMULTANEOUSLY PERFUSED STOMACH AND SMALL INTESTINE (3)			
pH	ASA ABSORPTION (micromol/100 mg protein/hr)		ASA SERUM LEVEL (mg/100 ml)
	STOMACH	SMALL BOWEL	
3.5	346	469	20.6
6.5	0	424	19.7

* From: Hollander D, et al. J Lab Clin Med 1981;98:591-8

VARIATION IN INTESTINAL pH



PATTERNS OF GASTRIC MOTOR ACTIVITY

- **FASTING** ***(CYCLICAL PATTERN < 2 HR)***

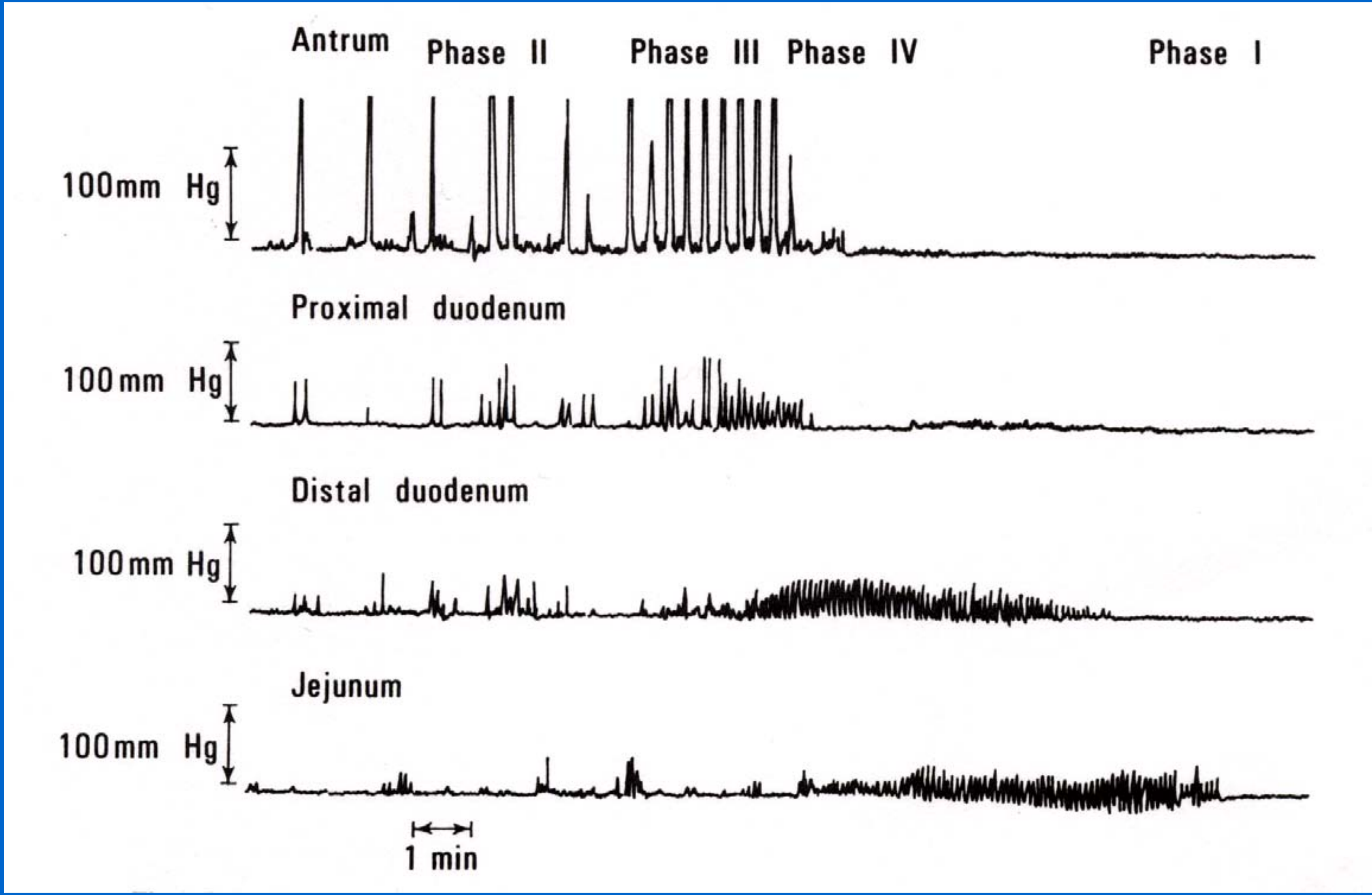
  PHASE 1 - QUIESENCE

  PHASE 2 - IRREGULAR CONTRACTIONS

  PHASE 3 - MAJOR MOTOR COMPLEX BURST

  PHASE 4 - TRANSITION PERIOD

HUMAN INTERDIGESTIVE MOTOR ACTIVITY*



*From: Rees WDW, et al. Dig Dis Sci 1982;27:321-9.

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  PHASE 1 - QUIESENCE

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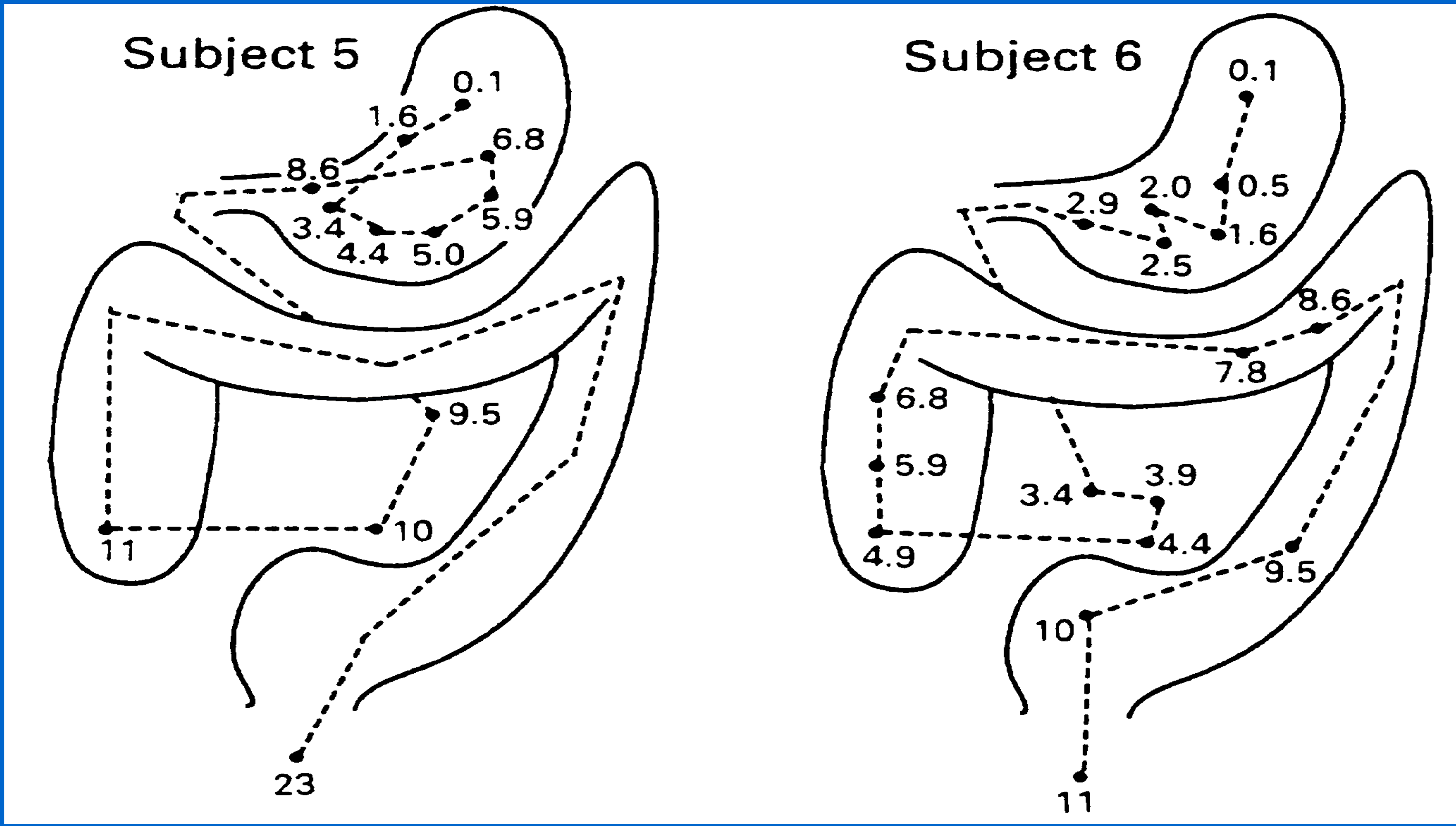
  PHASE 4 - TRANSITION PERIOD

- **POST PRANDIAL** ***(UP TO 10 HR DELAY)***

  - PYLORUS CONSTRICTED

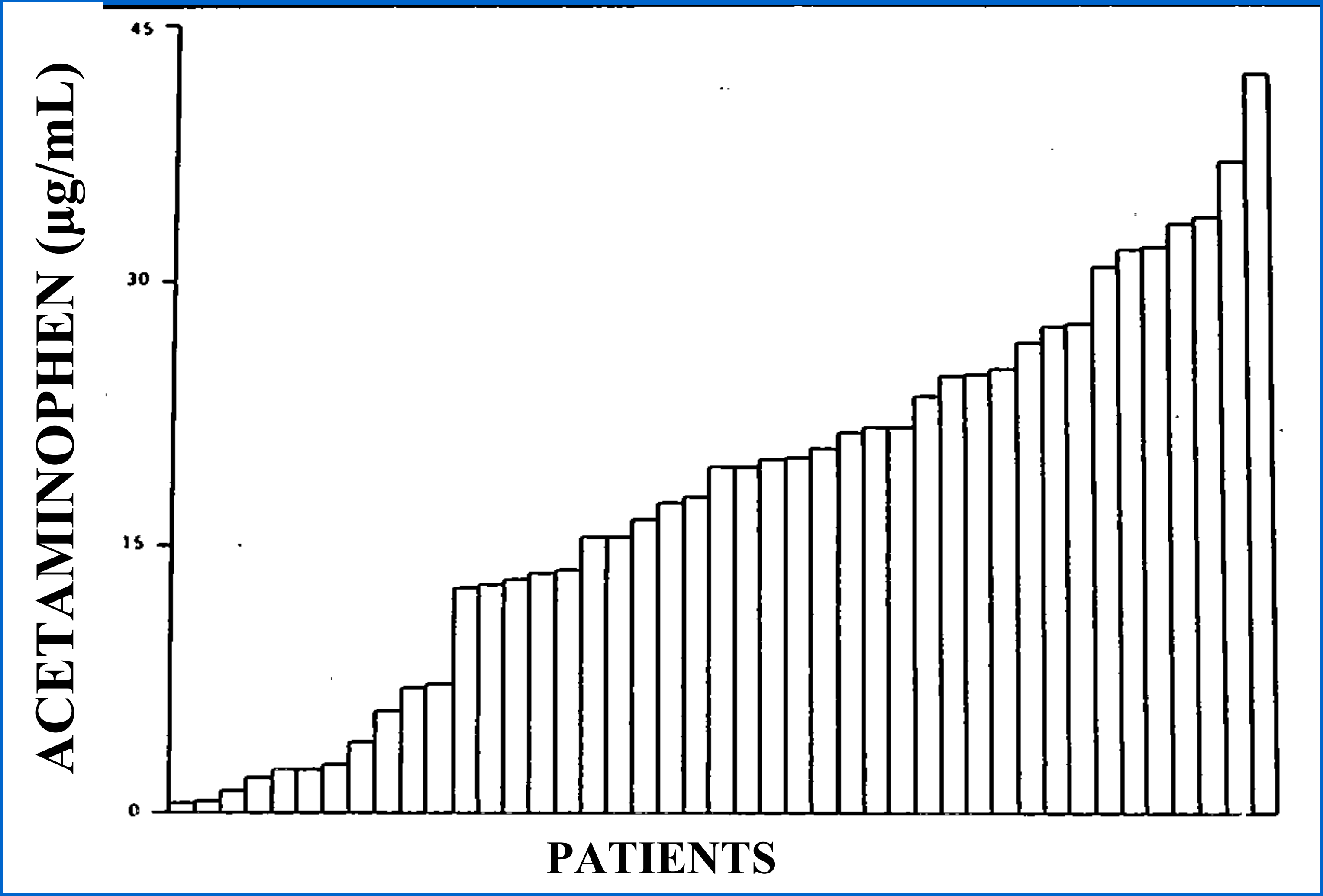
  - ANTRAL CONTRACTIONS REDUCE PARTICLE SIZE

GI TRANSIT OF A SUSTAINED-RELEASE CARBAMAZEPINE FORMULATION*

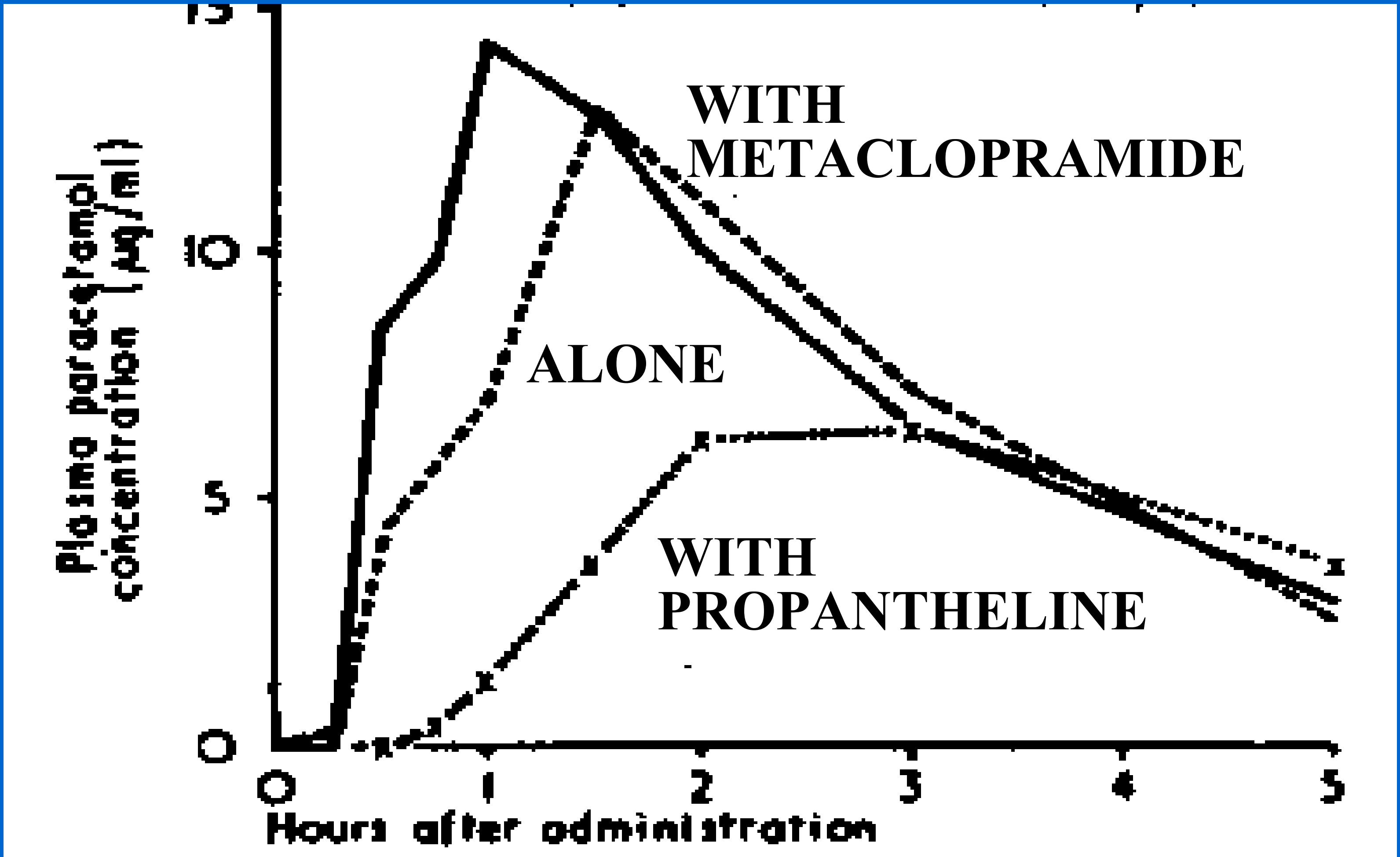


*From: Wilding IR, et al. Br J Clin Pharmacol 1991;32:573-9.

VARIATION IN PEAK ACETAMINOPHEN LEVELS

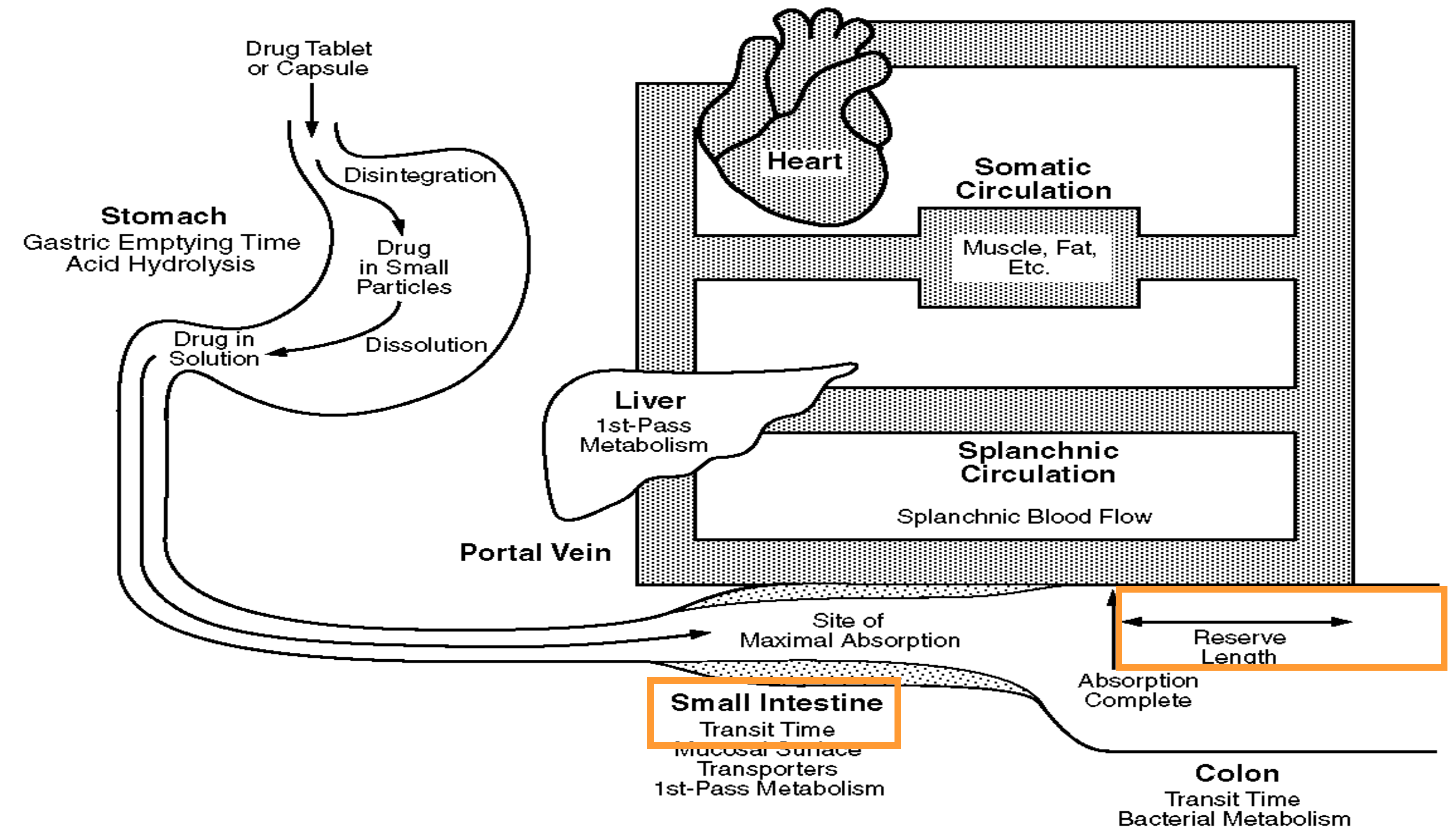


GASTRIC EMPTYING RATE AFFECTS ACETAMINOPHEN ABSORPTION*



*From: Nimmo J, et al. Br Med J 1973;1:587-9.

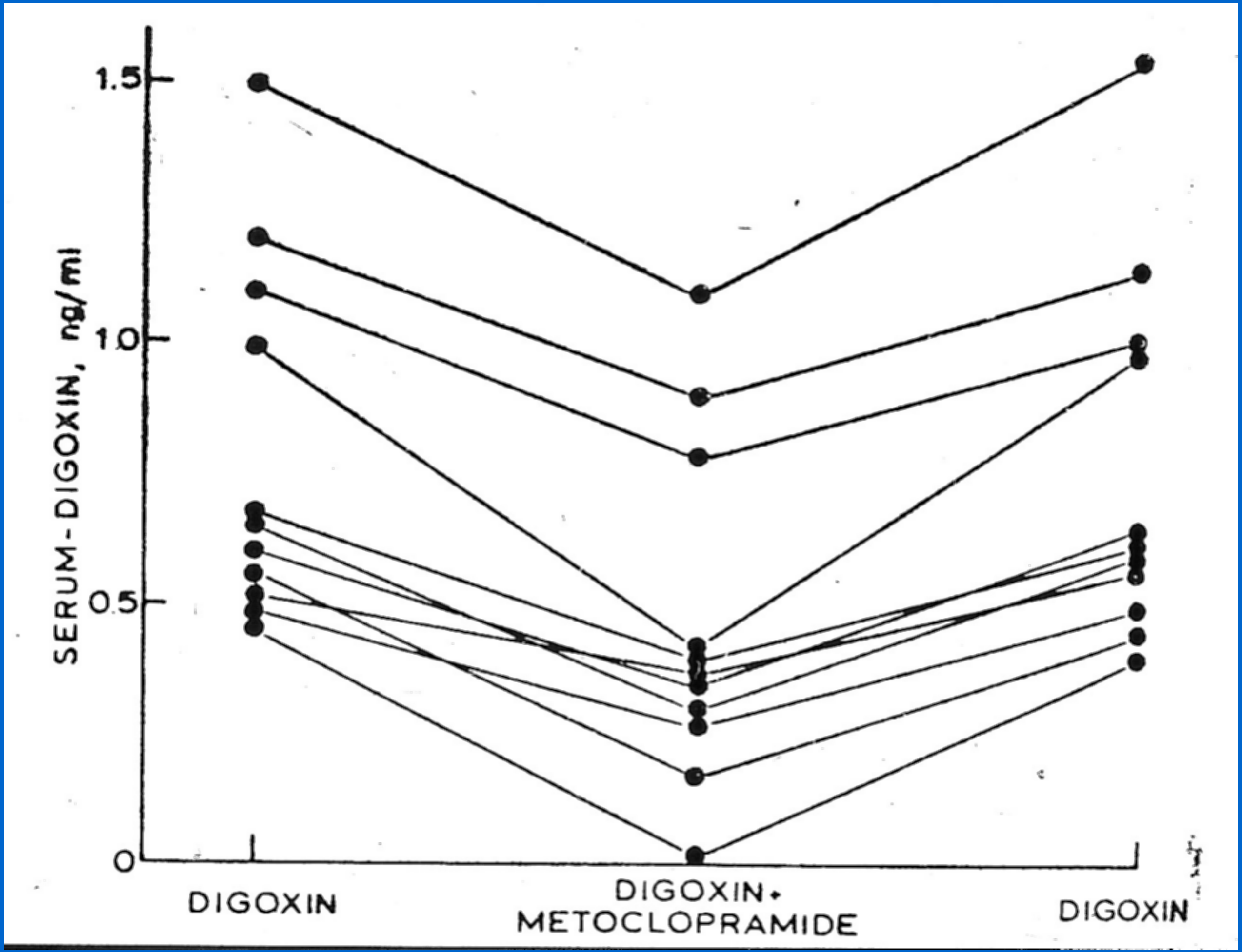
FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION



RESERVE LENGTH

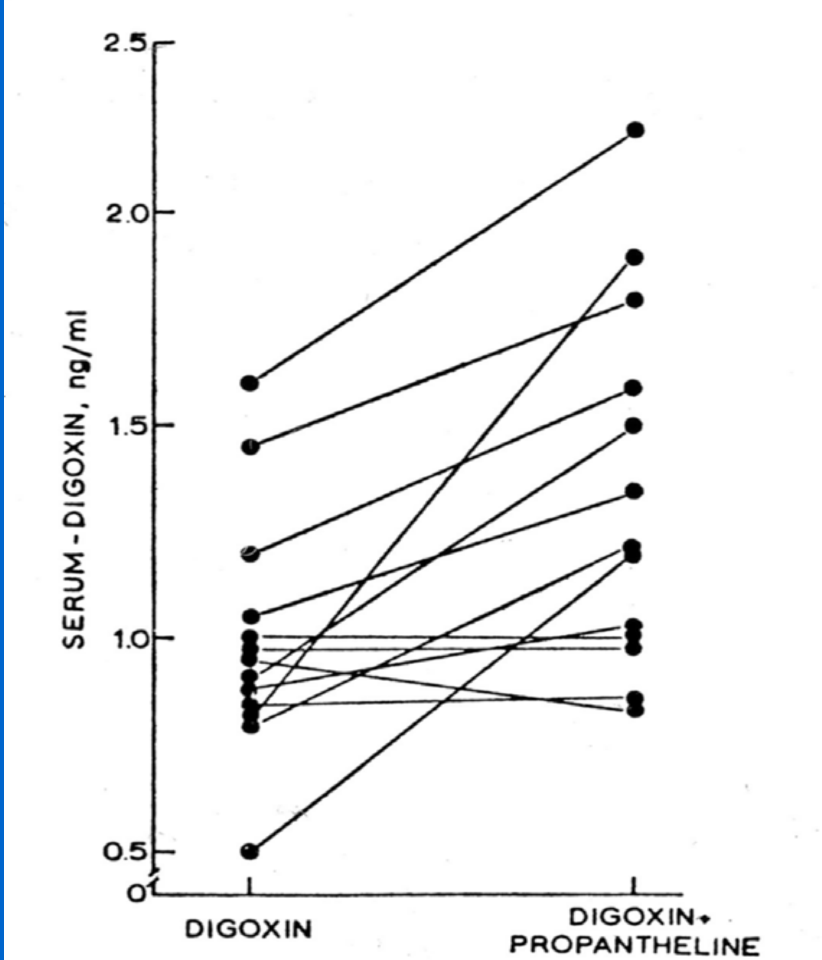
RESERVE LENGTH IS THE ANATOMICAL LENGTH OVER WHICH ABSORPTION OF A DRUG CAN OCCUR *MINUS* THE LENGTH AT WHICH ABSORPTION IS COMPLETE

EFFECT OF METACLOPRAMIDE ON DIGOXIN ABSORPTION*



*From: Manninen V, et al. Lancet 1973;1:398-99.

EFFECT OF PROPANTHELINE ON DIGOXIN ABSORPTION*



*From: Manninen V, et al. Lancet 1973;1:398-99.

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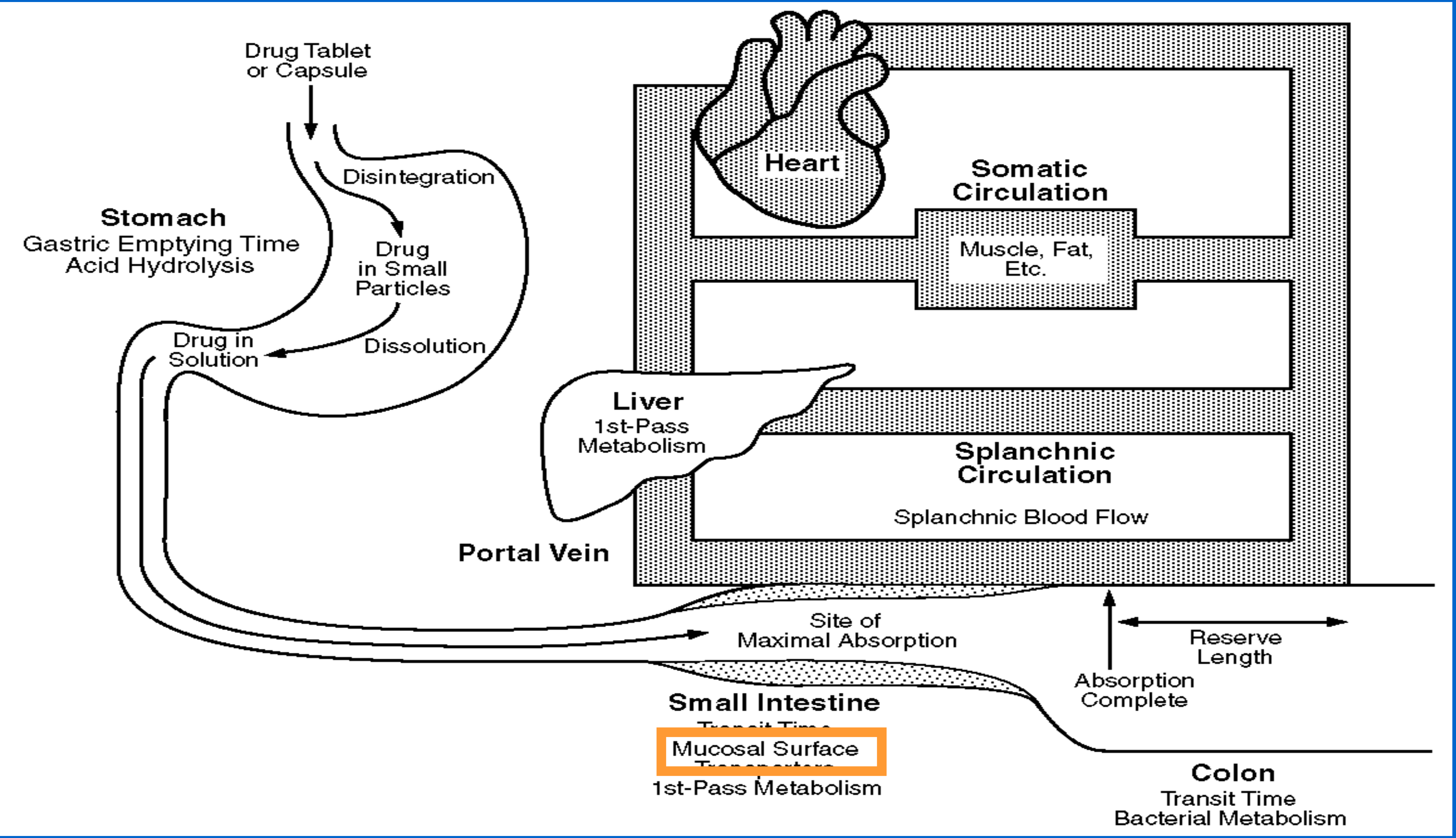
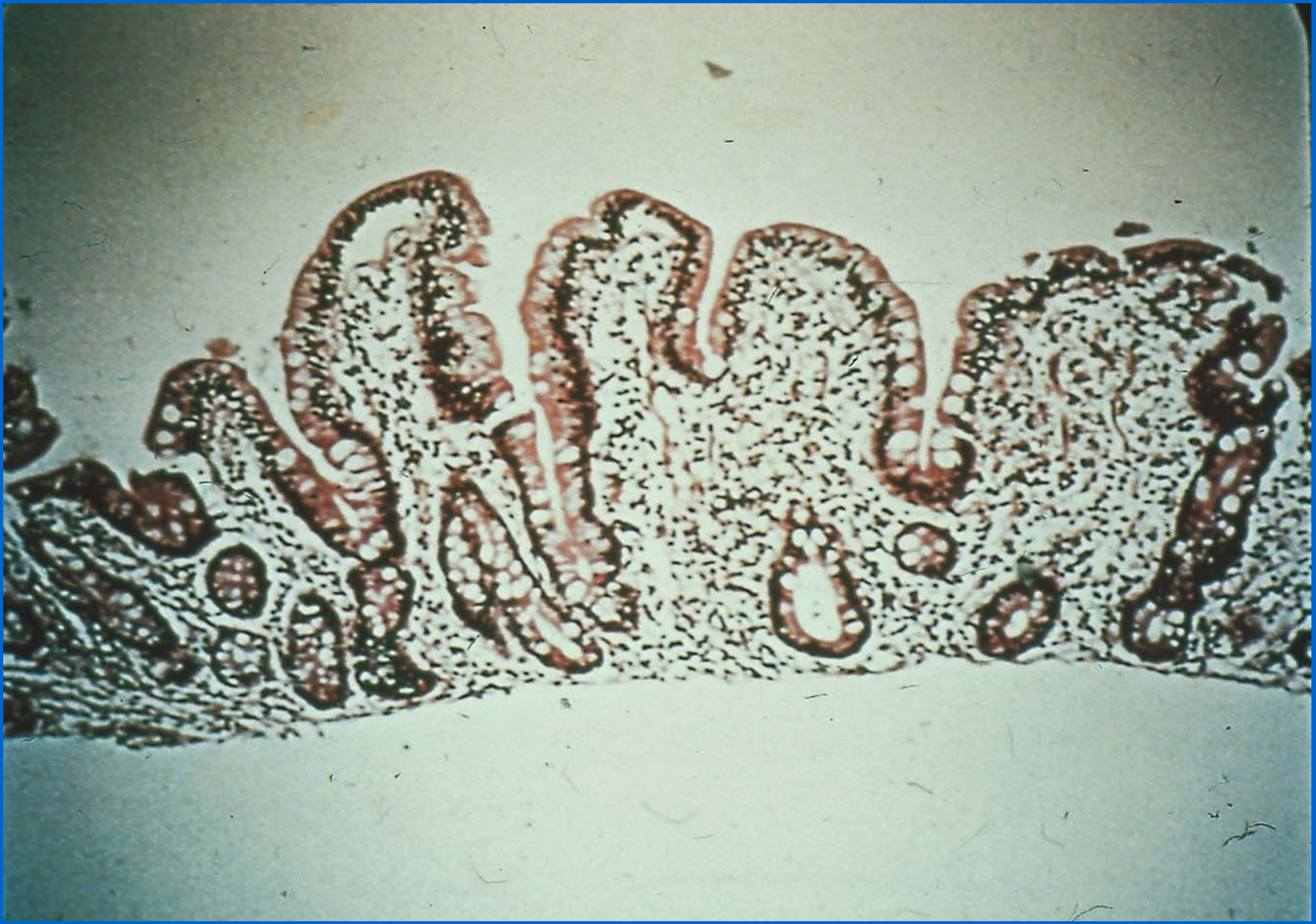


NORMAL INTESTINAL VILLI

BROAD INTESTINAL VILLI IN PATIENT WITH SPRUE



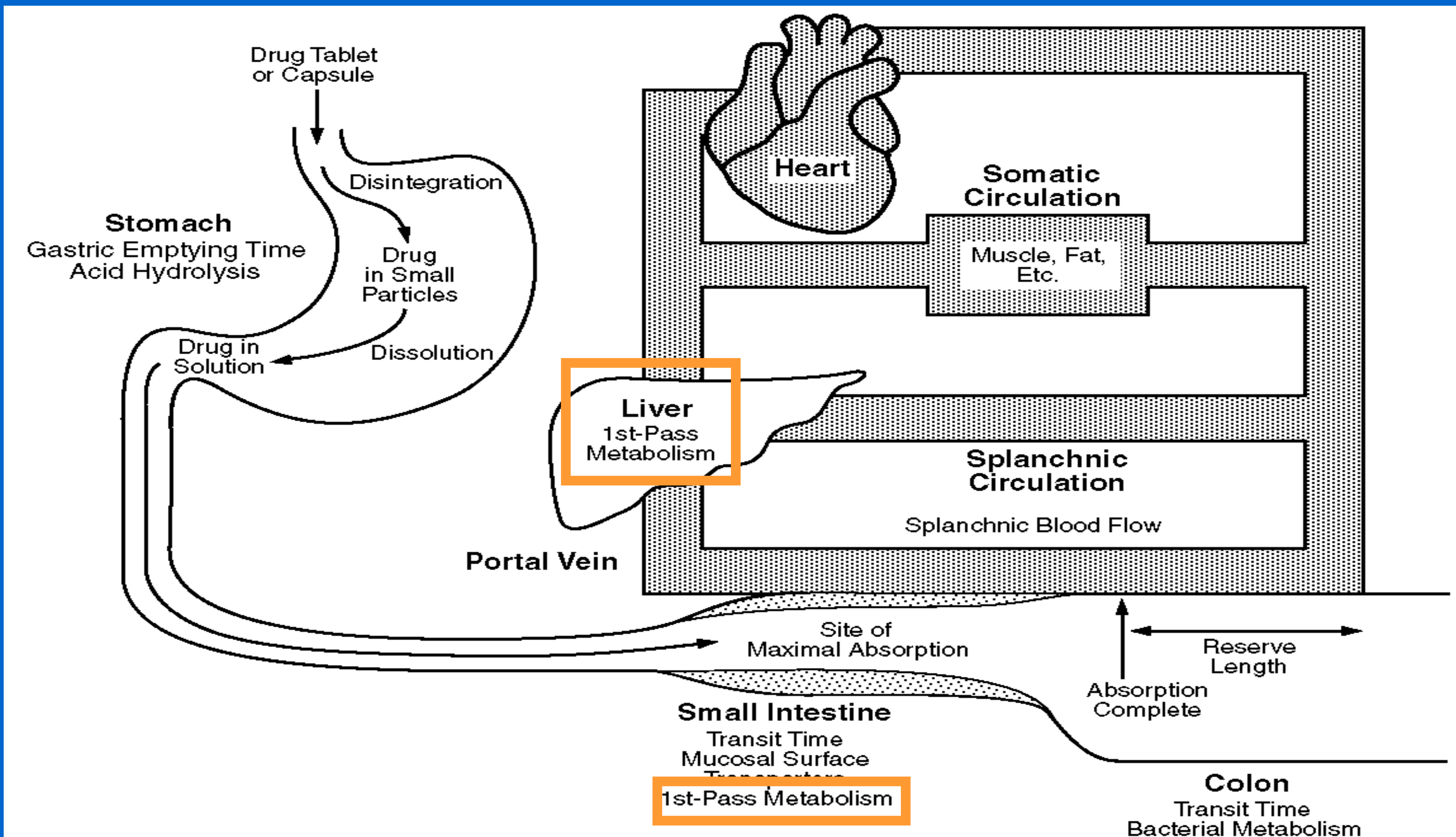
DIGOXIN LEVELS IN PATIENTS WITH INTESTINAL MALABSORPTION*

	CONTROLS	MALABSORPTION
[DIGOXIN] (ng/mL)	1.3 ± 0.3	0.4 ± 0.3
URINE D-XYLOSE EXCRETION (gm/5 hr)	5 – 8 †	1.1 – 4.1

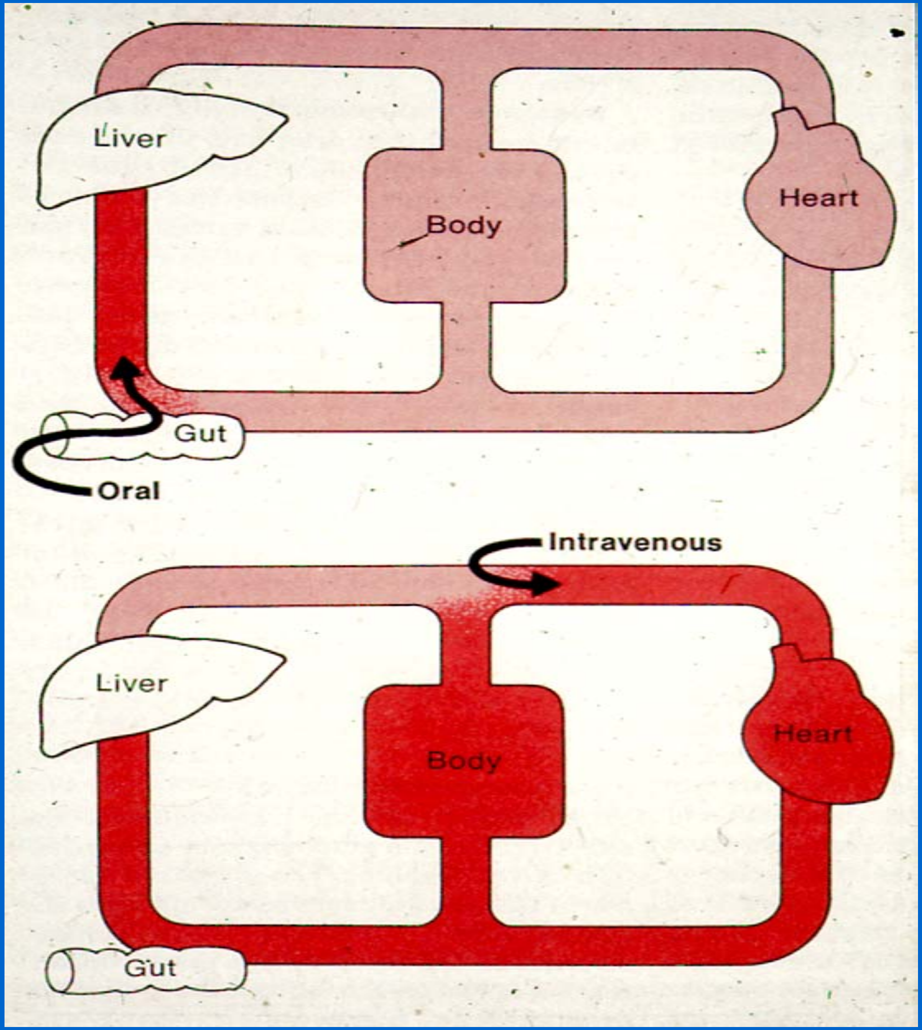
† NORMAL RANGE

* From: Heizer WD, et al. N Engl J Med 1971;285:257-9.

FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION



FIRST-PASS METABOLISM



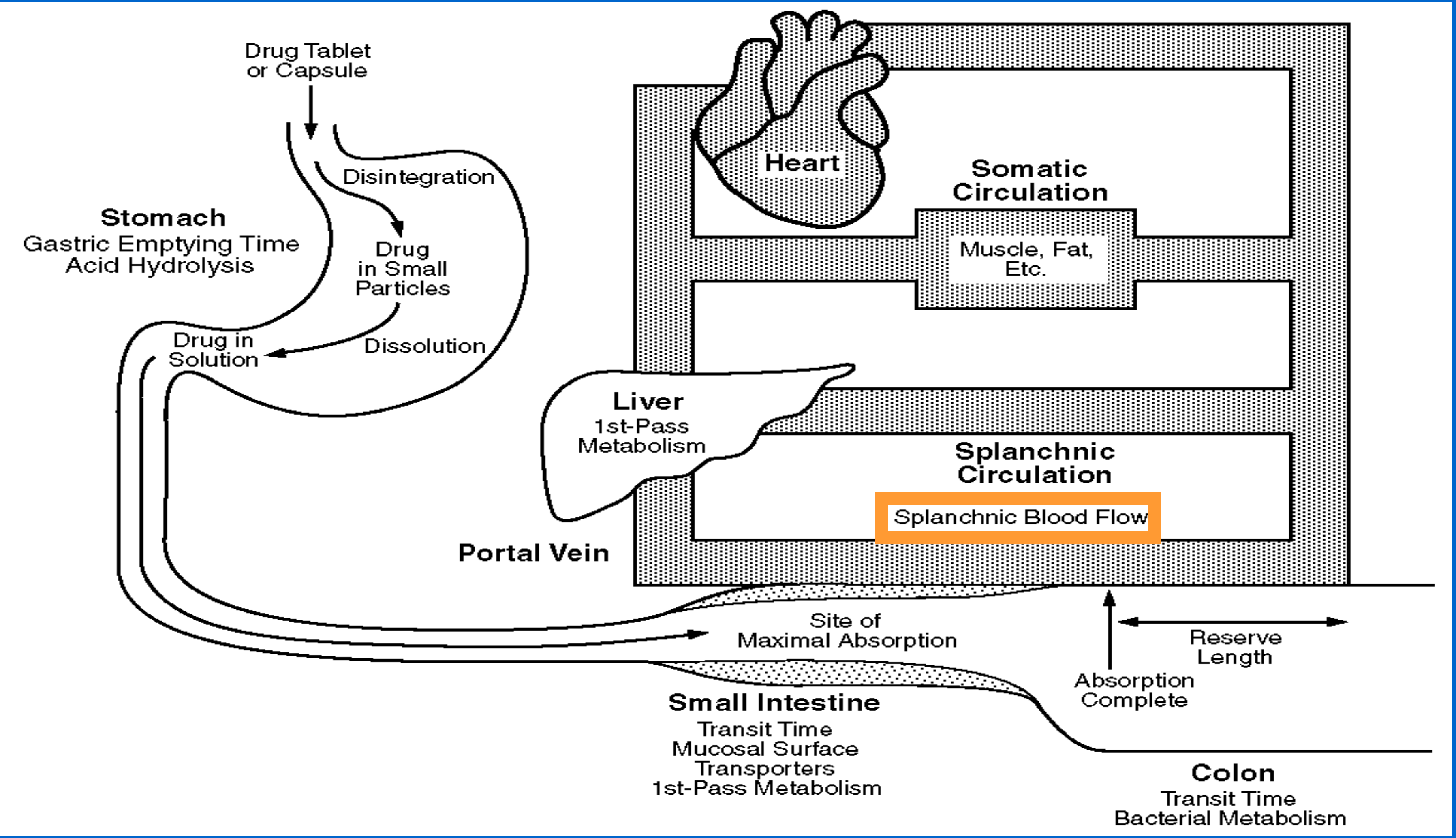
DRUGS WITH FIRST-PASS METABOLISM OR P-GLYCOPROTEIN TRANSPORT

ALDOSTERONE	MORPHINE
CYCLOSPORINE	NORTRIPTYLINE
ISOPROTERENOL	ORGANIC NITRATES
LIDOCAINE	PROPRANOLOL

SITES OF FIRST-PASS ELIMINATION

- INTESTINAL MUCOSA
  - P-GLYCOPROTEIN
  - CYP ENZYMES
- LIVER
  - CYP ENZYMES

FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION



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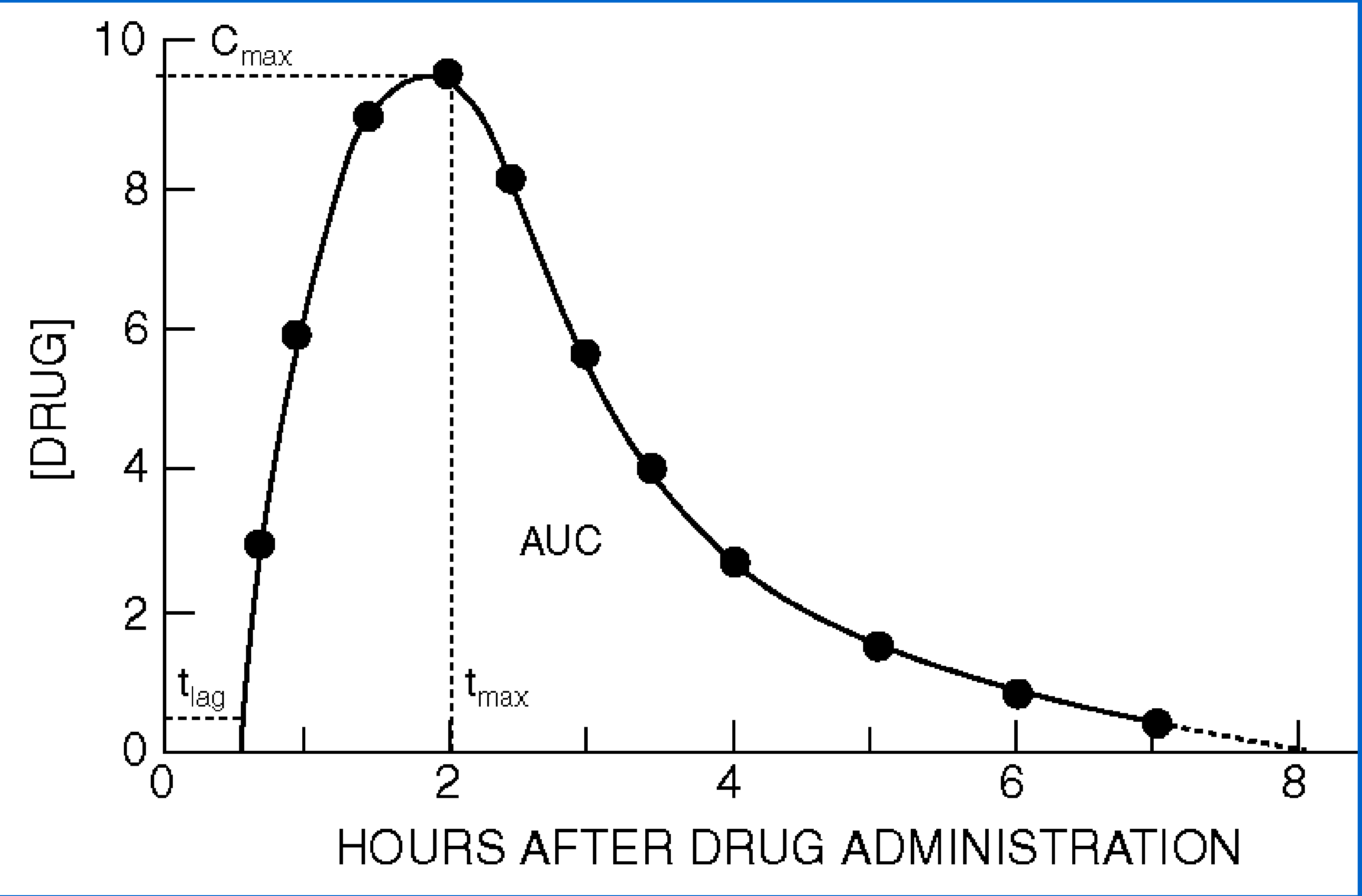
BIOAVAILABILITY

BIOAVAILABILITY IS THE *RELATIVE AMOUNT* OF A DRUG DOSE THAT REACHES THE SYSTEMIC CIRCULATION UNCHANGED AND THE *RATE* AT WHICH THIS OCCURS.

SERUM CONCENTRATION-TIME CURVE AFTER A SINGLE ORAL DOSE



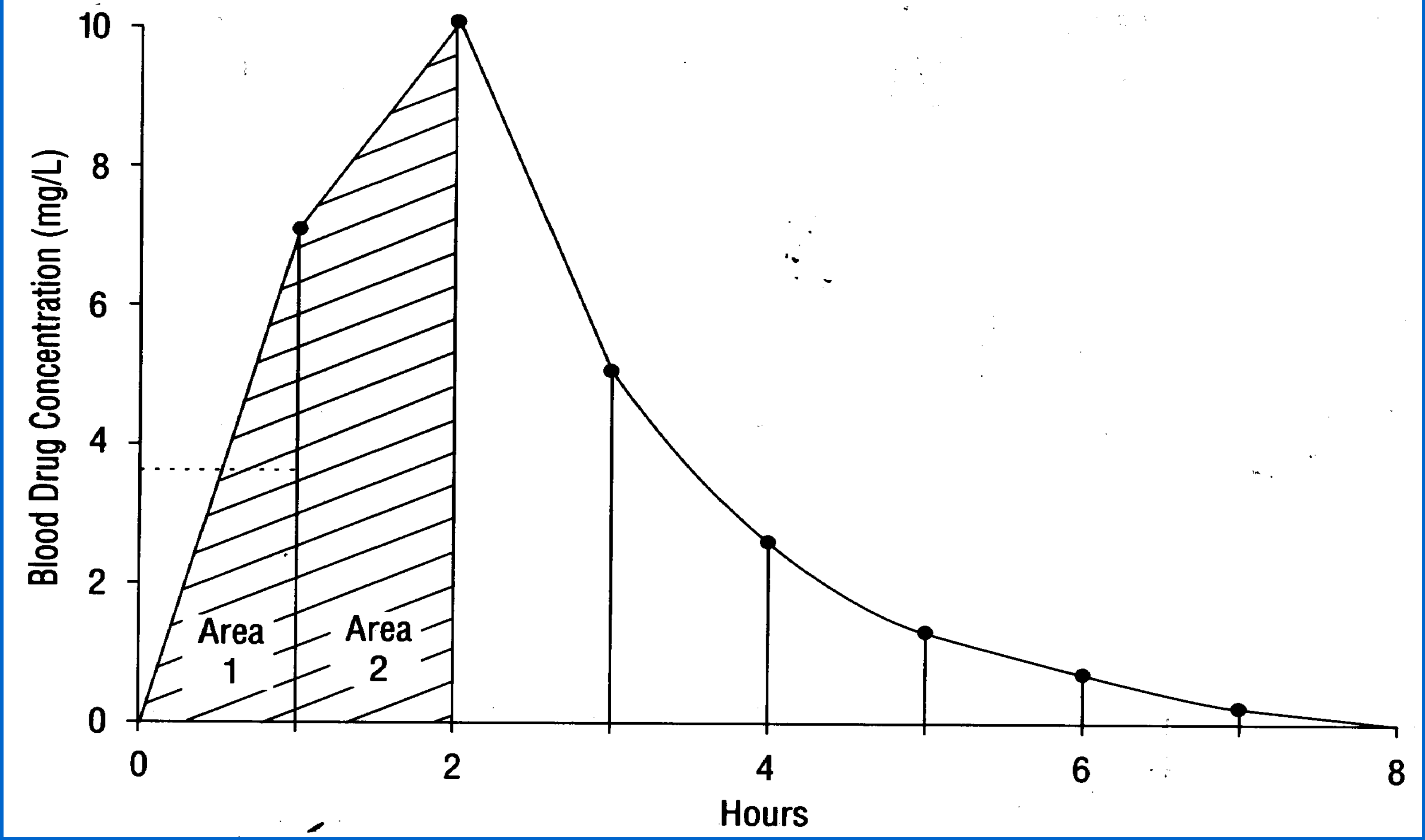
SIGNIFICANCE OF AUC

$$dE/dt = CL_E \bullet C$$

$$E = CL_E \int_0^\infty C \, dt$$

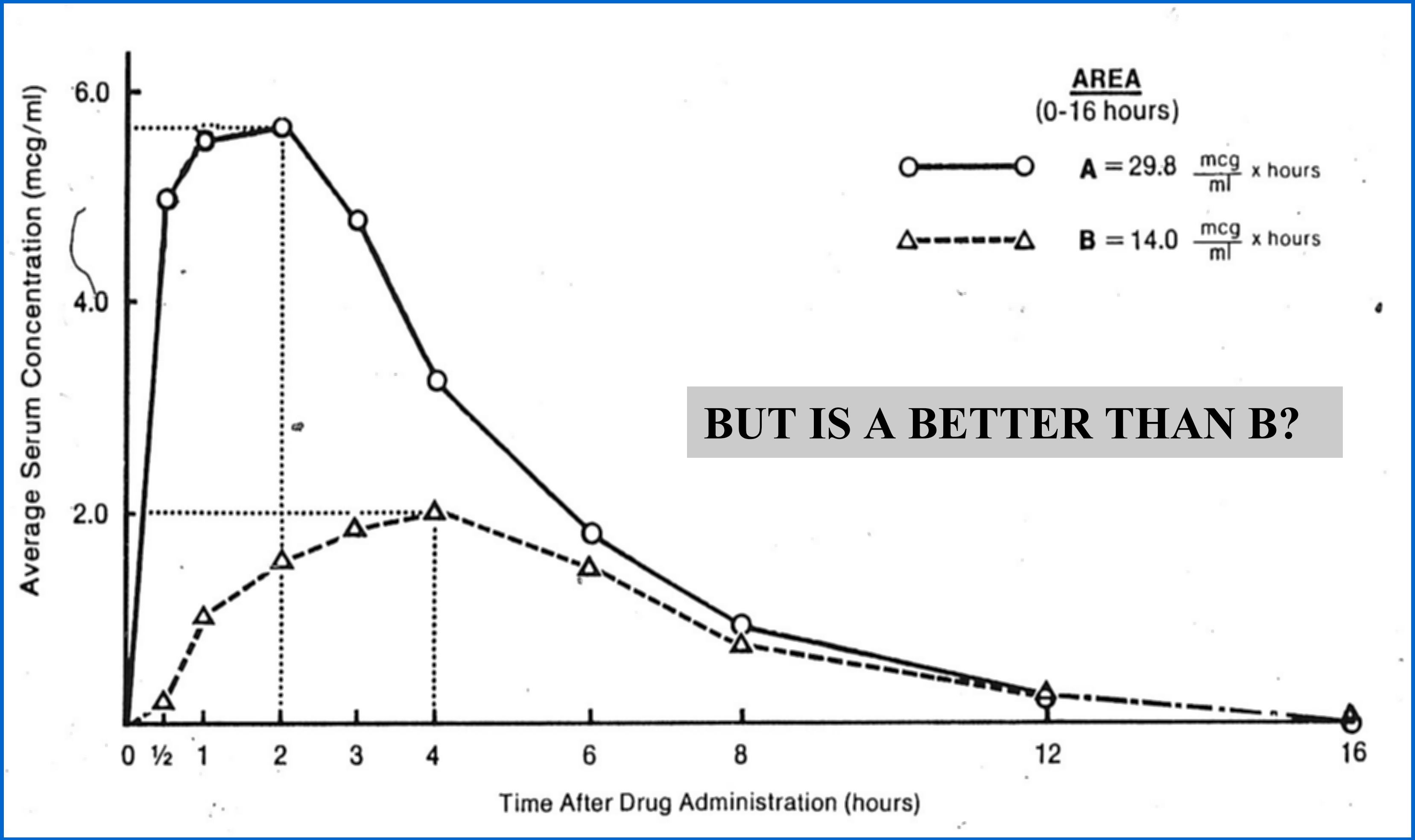
$$D \bullet F = CL_E \bullet AUC$$

CALCULATION OF AUC BY TRAPEZOIDAL RULE*



From: Rowland M, Tozer TN. Clinical Pharmacokinetics. p 470.

AUC A > B



BUT IS A BETTER THAN B?

ABSOLUTE BIOAVAILABILITY

$$\% \text{ Absorption} = \frac{D_{IV} \bullet AUC_{oral}}{D_{oral} \bullet AUC_{IV}} \times 100$$

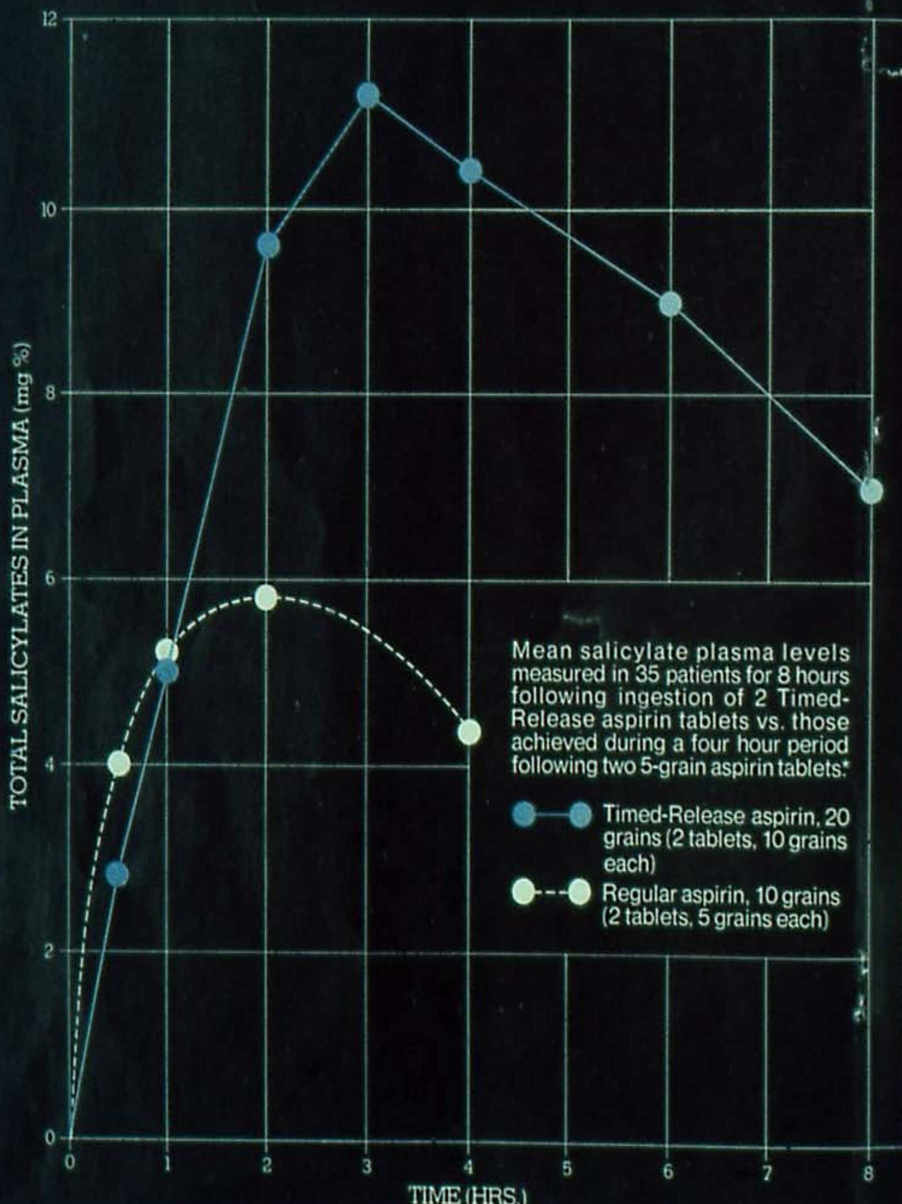
COMPARISON HERE IS BETWEEN AN ORAL AND AN IV FORMULATION.

RELATIVE BIOAVAILABILITY

$$\%\ \text{Relative B.A.} = \frac{D_{\text{Ref.}} \bullet AUC_{\text{Test}}}{D_{\text{Test}} \bullet AUC_{\text{Ref.}}} \times 100$$

COMPARISON HERE IS BETWEEN TWO ORAL FORMULATIONS

How to keep salicylate blood levels up ...even when your arthritis patient isn't.



A shift at bedtime from Bayer* 5-grain Aspirin to Bayer* Timed-Release Aspirin can help maintain the consistent serum salicylate levels so important for control of arthritic inflammation and pain—*without the need to interrupt sleep.*

Formulated especially for use in arthritis, this exclusive 8-hour dosage form provides 10 grains (650 mg) of microencapsulated aspirin in each tablet. While patients sleep, aspirin is released systematically into the bloodstream. Salicylate levels and anti-inflammatory activity are prolonged and patients should experience less nighttime awakening due to pain and arise freer of discouraging morning stiffness.

So during the day, when arthritis patients are up to take medication on schedule, recommend Bayer 5-grain Aspirin. But during the sleeping hours, for extended analgesic and anti-inflammatory activity, recommend Bayer Timed-Release Aspirin, 2 tablets, h.s. It provides all the advantages of aspirin ... throughout the night.

The night "shift" in arthritis therapy

Bayer Timed-Release Aspirin

The Bayer Company
Glenbrook Laboratories, Division of Sterling Drug Inc.
90 Park Avenue, New York, New York 10016

RELATIVE BIOAVAILABILITY

$$\%\ \text{Relative B.A.} = \frac{D_{\text{Ref.}} \bullet AUC_{\text{Test}}}{D_{\text{Test}} \bullet AUC_{\text{Ref.}}} \times 100$$

AUC VALUES HAVE TO BE NORMALIZED FOR DOSE.

ASSESSMENT OF DRUG ABSORPTION RATE

- AUC ESTIMATES CAN BE USED TO ESTIMATE EXTENT OF DRUG ABSORPTION.
- RECOVERY OF PARENT DRUG IN URINE CAN BE USED TO ESTIMATE EXTENT OF DRUG ABSORPTION.
- HOW IS ABSORPTION RATE ASSESSED?
  - T_{MAX}
  - INTEGRATED PHARMACOKINETIC ANALYSIS OF ABSOLUTE BIOAVAILABILITY.

BIOAVAILABILITY FROM RENAL EXCRETION OF UNCHANGED DRUG

$$\text{Since: } F \bullet D = E \quad \text{and } E = \left(\frac{CL_E}{CL_R}\right) E_R$$

$$F \bullet D_{oral} = \left(\frac{CL_E}{CL_R}\right) E_{R(oral)} \quad \text{and } D_{IV} = \left(\frac{CL_E}{CL_R}\right) E_{R(IV)}$$

$$\text{So: } \%\ \text{Absorption} = \frac{D_{IV} \bullet E_{R(oral)}}{D_{oral} \bullet E_{R(IV)}} \text{ X } 100$$

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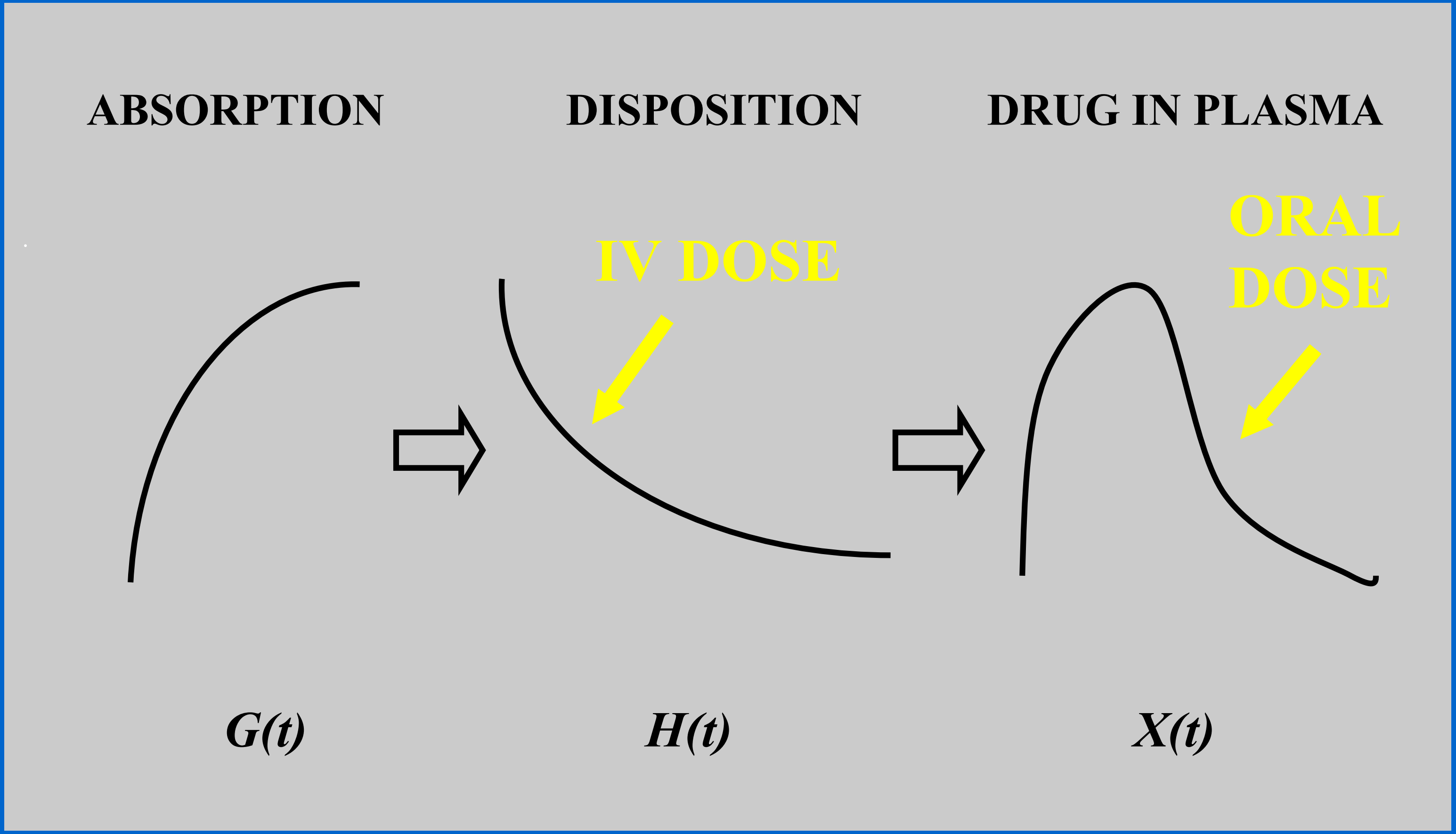
INTERACTION OF DRUG ABSORPTION AND DISPOSITION PROCESSES



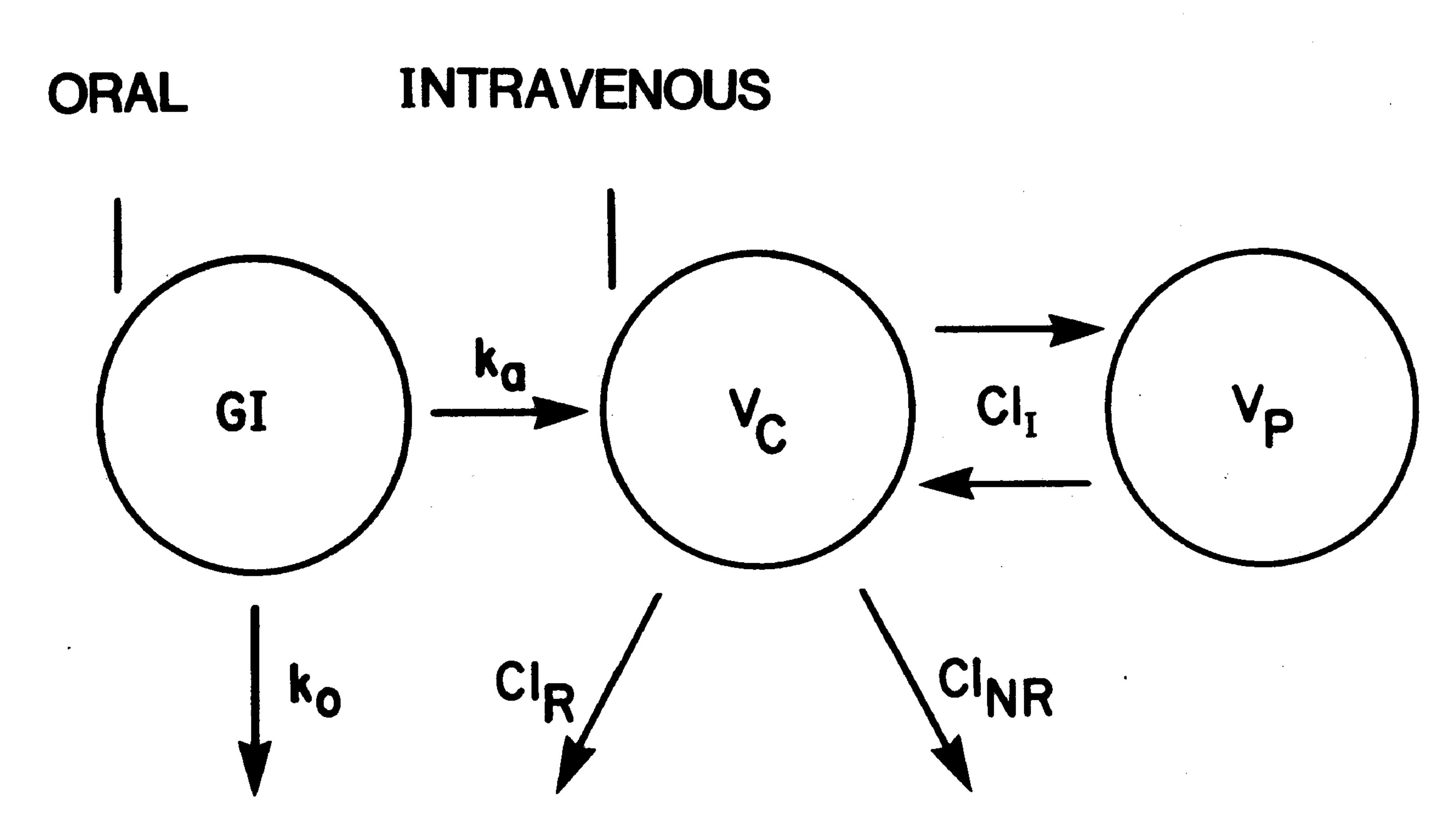
THE OPERATION OF CONVOLUTION

INTEGRAL FORM : $X(t) = \int_0^t G(\tau) \bullet H(t-\tau)\,d\tau$

TIME DOMAIN : $X(t) = G(t) * H(t)$

SUBSIDIARY EQUATION : $x(s) = g(s) \bullet h(s)$

MODEL USED TO ANALYZE KINETICS OF DRUG ABSORPTION



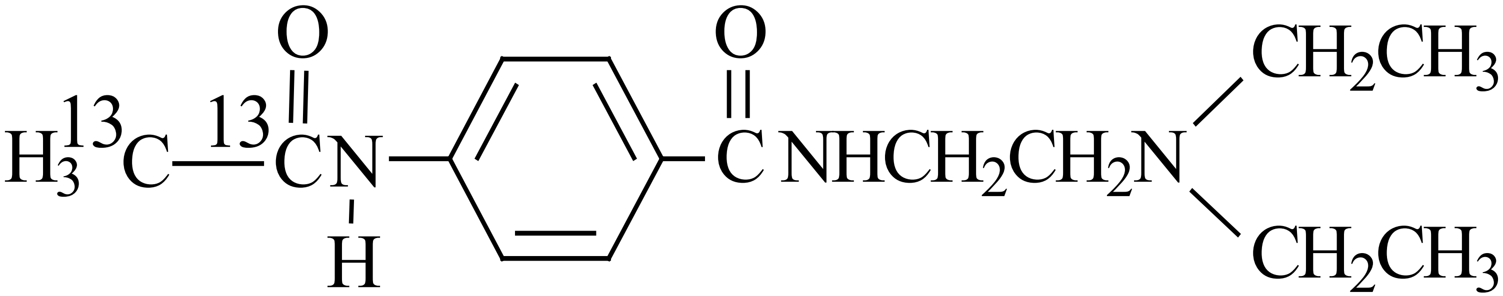
CALCULATION OF BIOAVAILABILITY FROM FIRST-ORDER ABSORPTION MODEL

$$F = \frac{k_a}{k_a + k_o}$$

METHODS FOR ASSESSMENT OF ABSOLUTE BIOAVAILABILITY

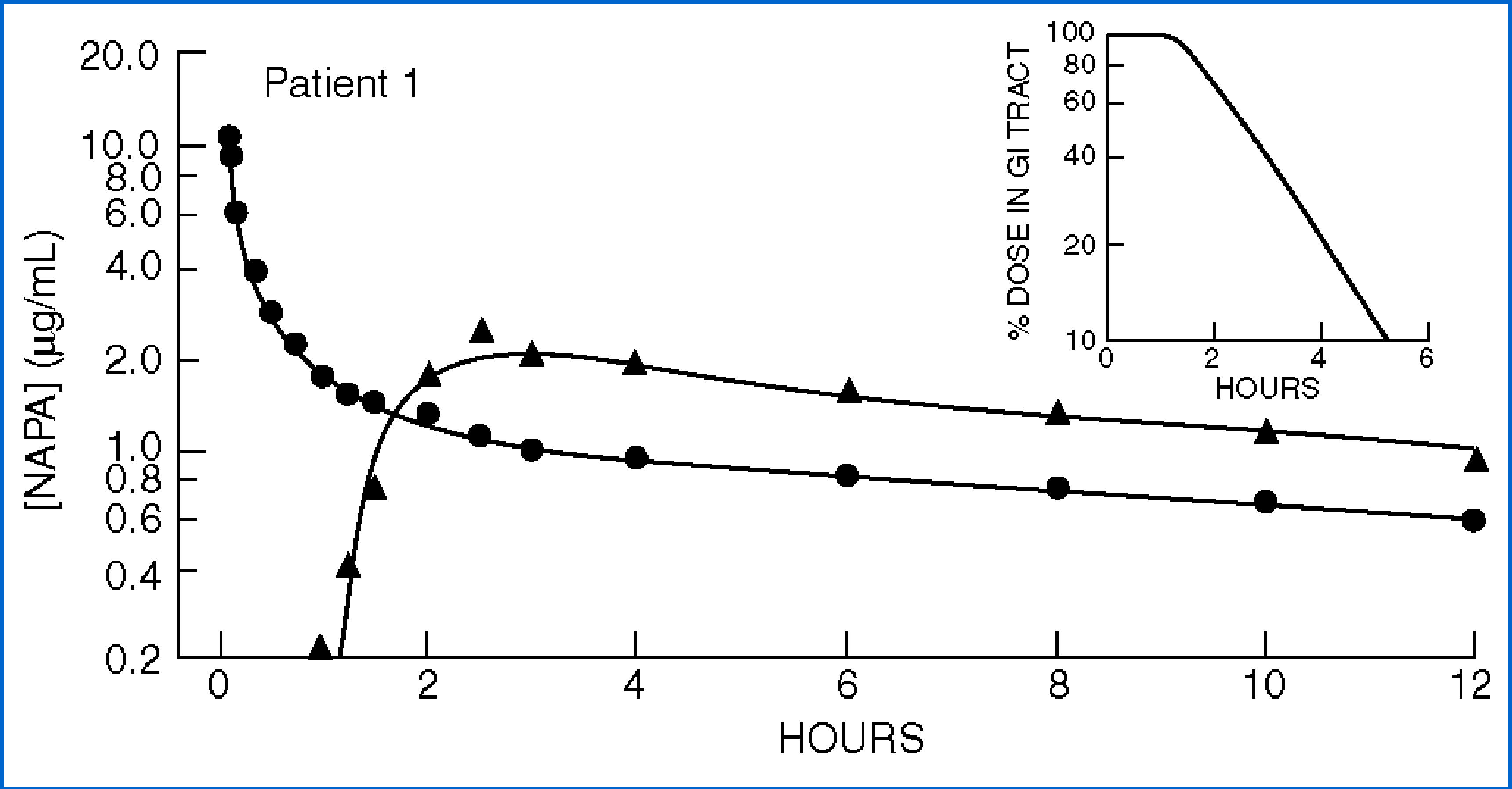
- CONVENTIONAL METHOD: IV AND ORAL DOSES USUALLY GIVEN ON TWO SEPARATE OCCASIONS
  - REQUIRES TWO STUDY SESSIONS
  - REQUIRES TWO SETS OF BLOOD SAMPLES
  - ASSUMES NO CHANGE IN DISPOSITION PARAMETERS BETWEEN STUDIES.
- STABLE ISOTOPE METHOD
  - ONE STUDY AND SET OF BLOOD SAMPLES
  - SPECIAL SYNTHESIS REQUIREMENTS
  - MASS SPECTROMETER ASSAY REQUIRED

NAPA-$^{13}C_2$



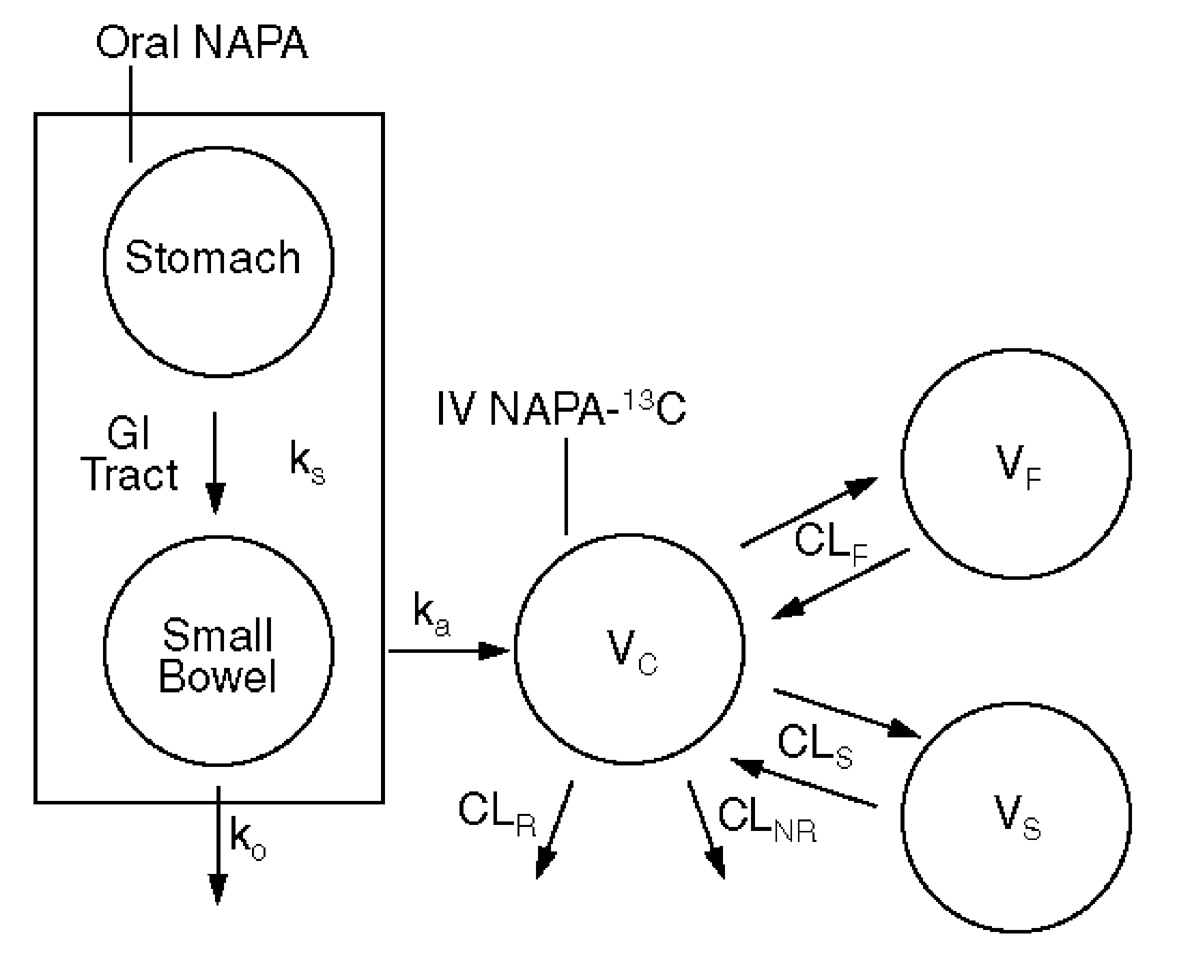
N **- ACETYLPROCAINAMIDE (NAPA -$^{13}C_2$)**

SIMULTANEOUS ADMINISTRATION OF ORAL NAPA AND IV NAPA-C^{13}*



* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.

MODEL USED TO ANALYZE ORAL NAPA AND IV NAPA-C13 KINETICS*



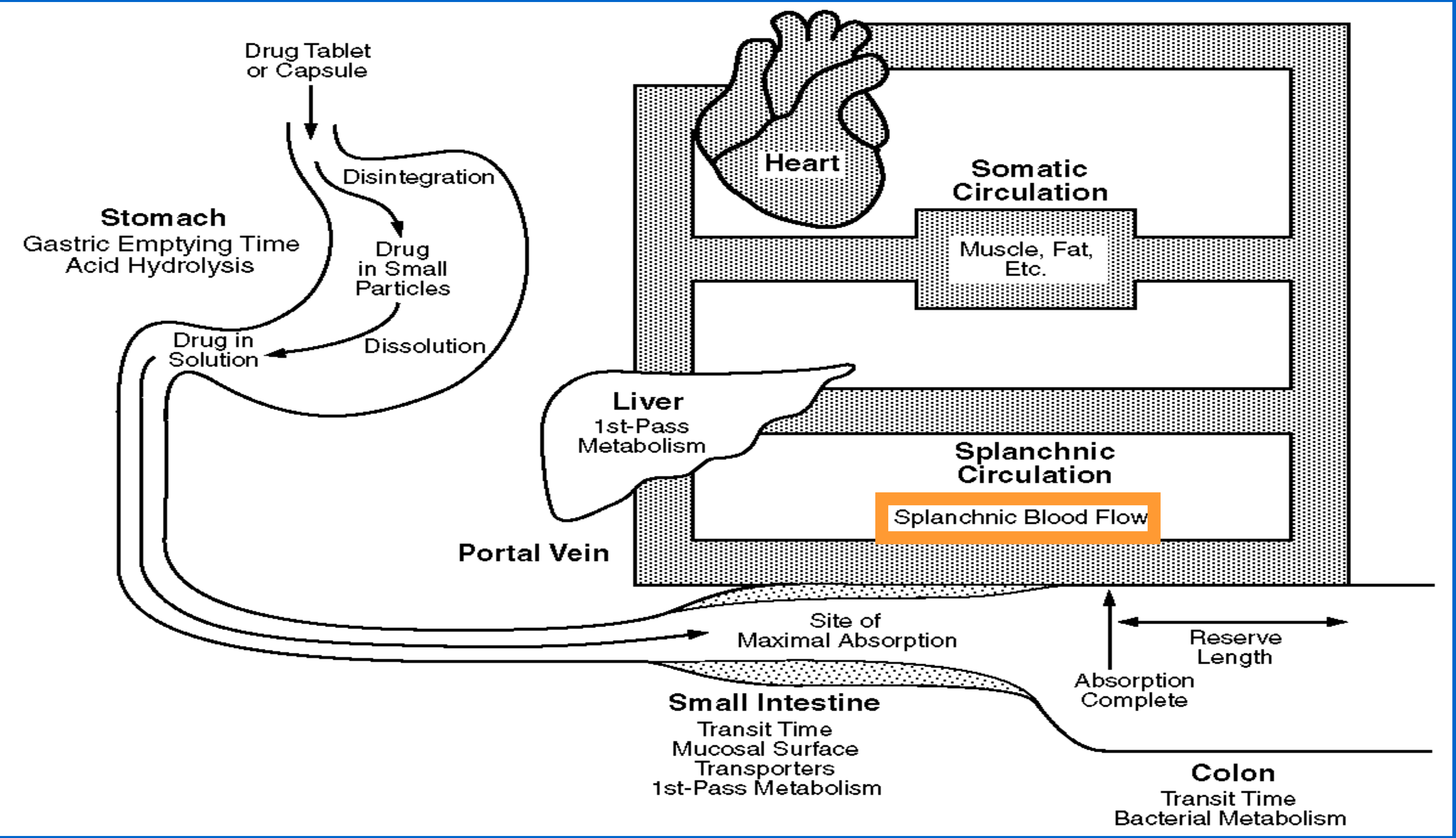
* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.

BIOAVAILABILITY ESTIMATES FROM KINETIC ANALYSIS AND URINE RECOVERY

PATIENT NUMBER	KINETIC ANALYSIS (%)	NAPA RECOVERY IN URINE* (%)
1	66.1	65.9
2	92.1	92.1
3	68.1	69.9
4	88.2	73.1
5	75.7	75.6

* Corrected for absorption lag time.

FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION



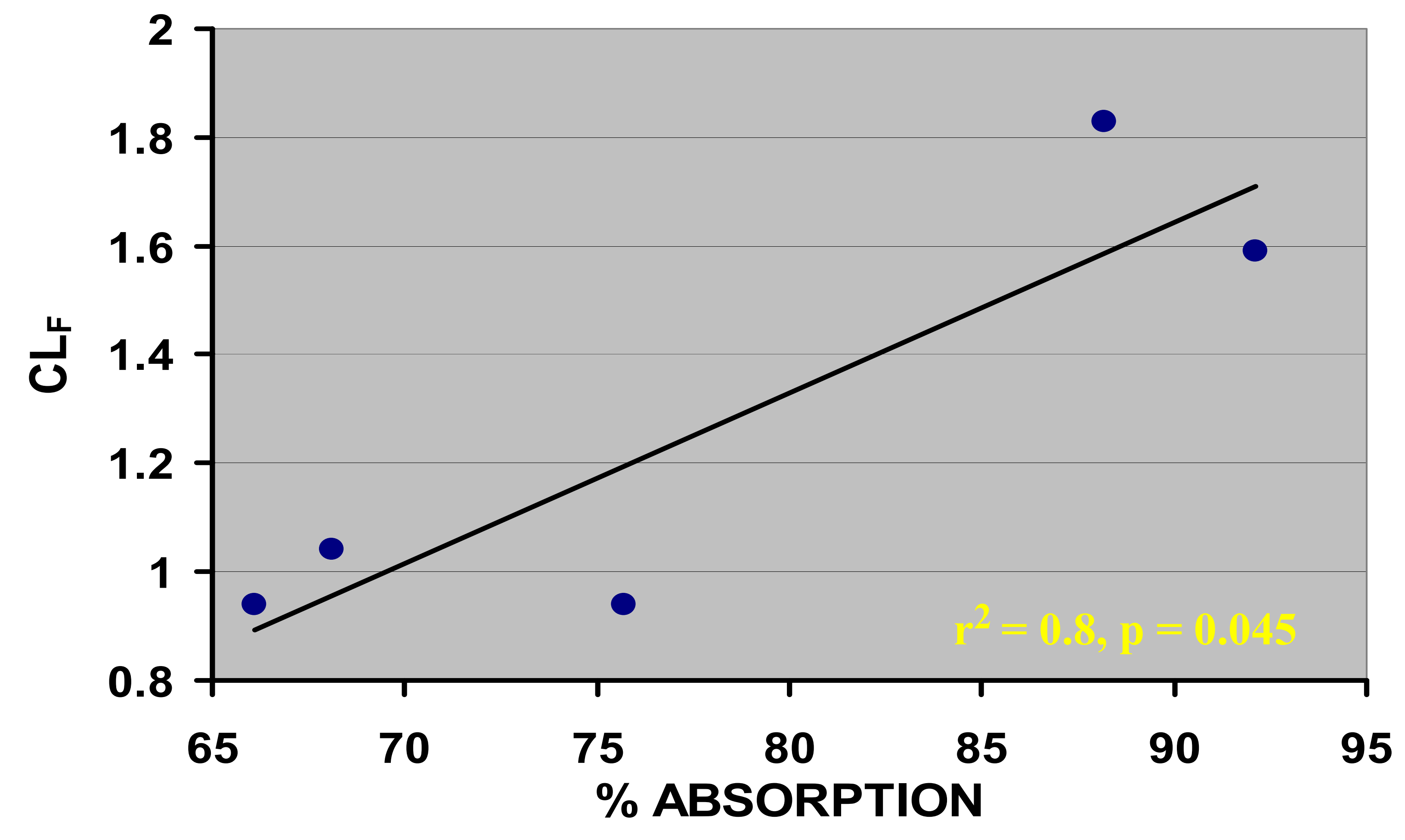
RENKIN EQUATION*

$$Cl = Q\left(1 - e^{-P/Q}\right)$$

FAST INTERCOMPARTMENTAL CLEARANCE IS TO SOME EXTENT DETERMINED BY SPLANCHNIC BLOOD FLOW.

* From Renkin EM. Am J Physiol 1953;183:125-36.

RELATIONSHIP BETWEEN CL_F AND EXTENT OF NAPA ABSORPTION*



* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.

THOUGHTS ABOUT ABSOLUTE BIOAVAILABILITY STUDIES

- ABSOLUTE BIOAVAILABILITY IS USUALLY STUDIED IN HEALTHY SUBJECTS, *NOT* IN THE PATIENT POPULATION FOR WHOM ITS USE IS INTENDED.
- THE STABLE ISOTOPE METHOD IS IDEALLY SUITED FOR STUDIES IN SPECIAL POPULATIONS (e.g. PEDIATRICS, PREGNANT WOMEN) AND OTHER PATIENT GROUPS.

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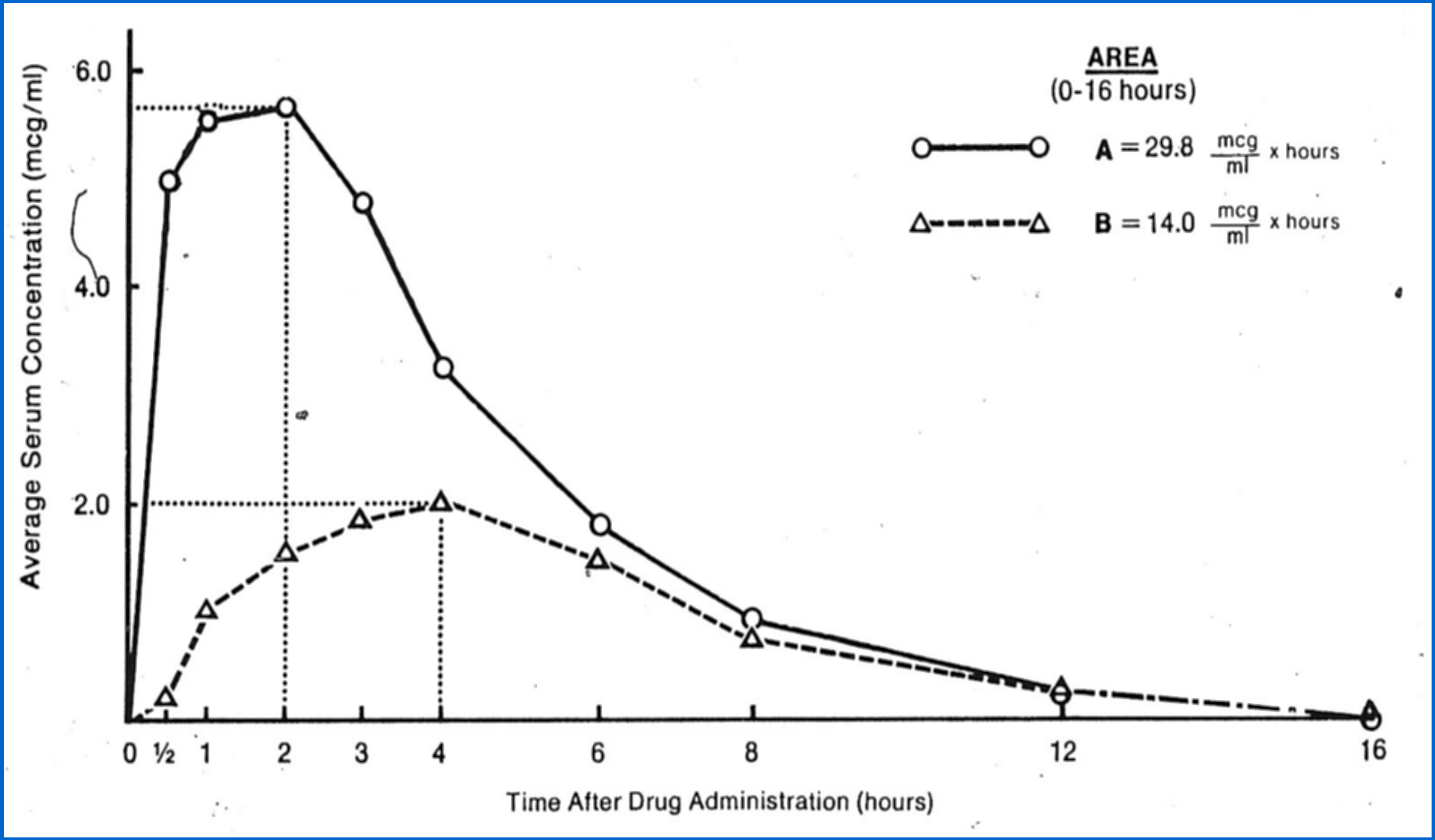
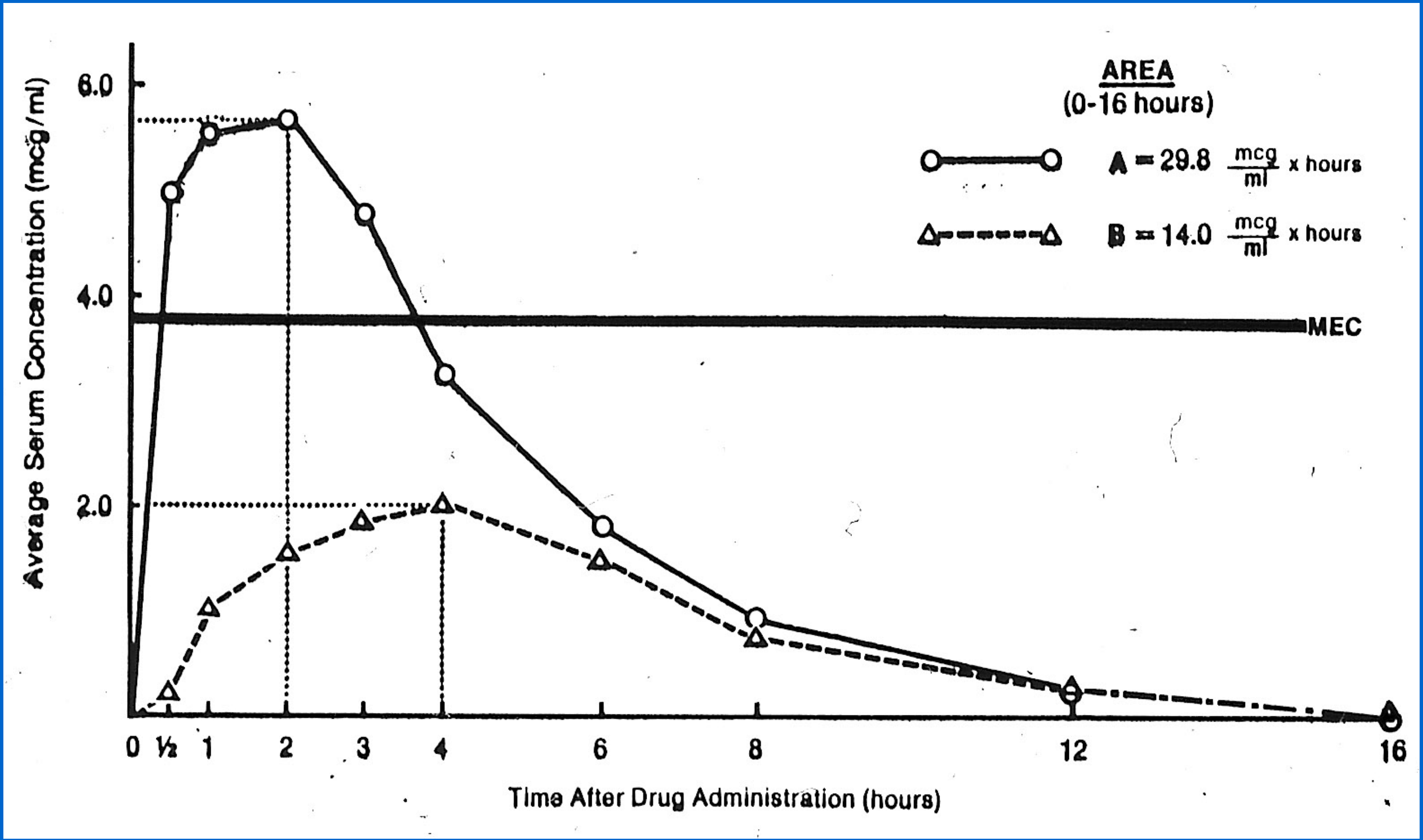
RELATIVE BIOAVAILABILITY TERMS

- **BIOEQUIVALENCE:** AUC & C_{MAX} WITHIN 80% - 125% OF REFERENCE COMPOUND
- **BIOINEQUIVALENCE:** GREATER DIFFERENCE IN BIOAVAILABILITY
- **THERAPEUTIC EQUIVALENCE:** SIMILAR CLINICAL EFFECTIVENESS & SAFETY
- **THERAPEUTIC INEQUIVALENCE:** IMPORTANT CLINICAL DIFFERENCE IN BIOAVAILABILITY

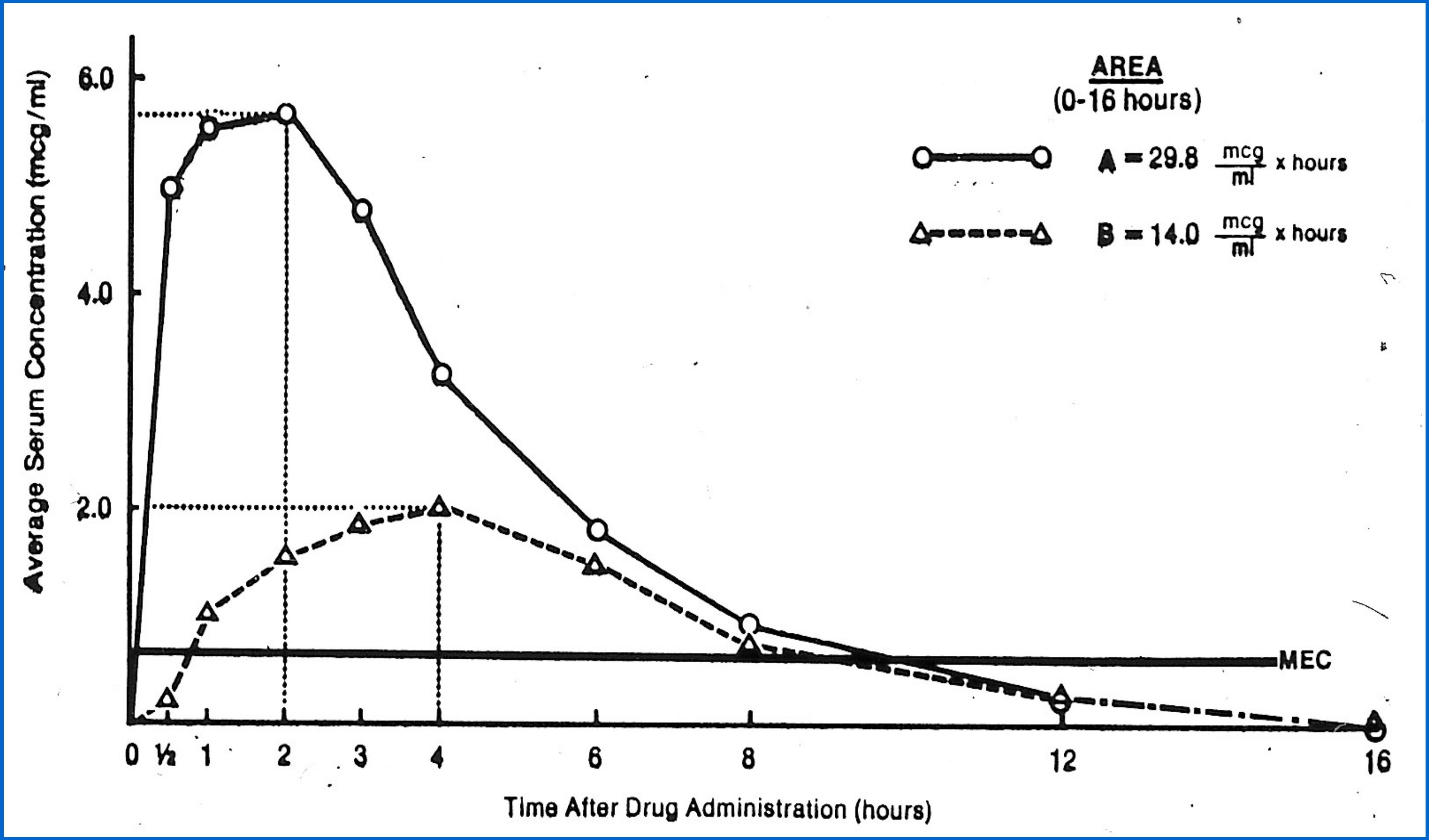
AUC A > B:
? THERAPEUTIC SIGNIFICANCE



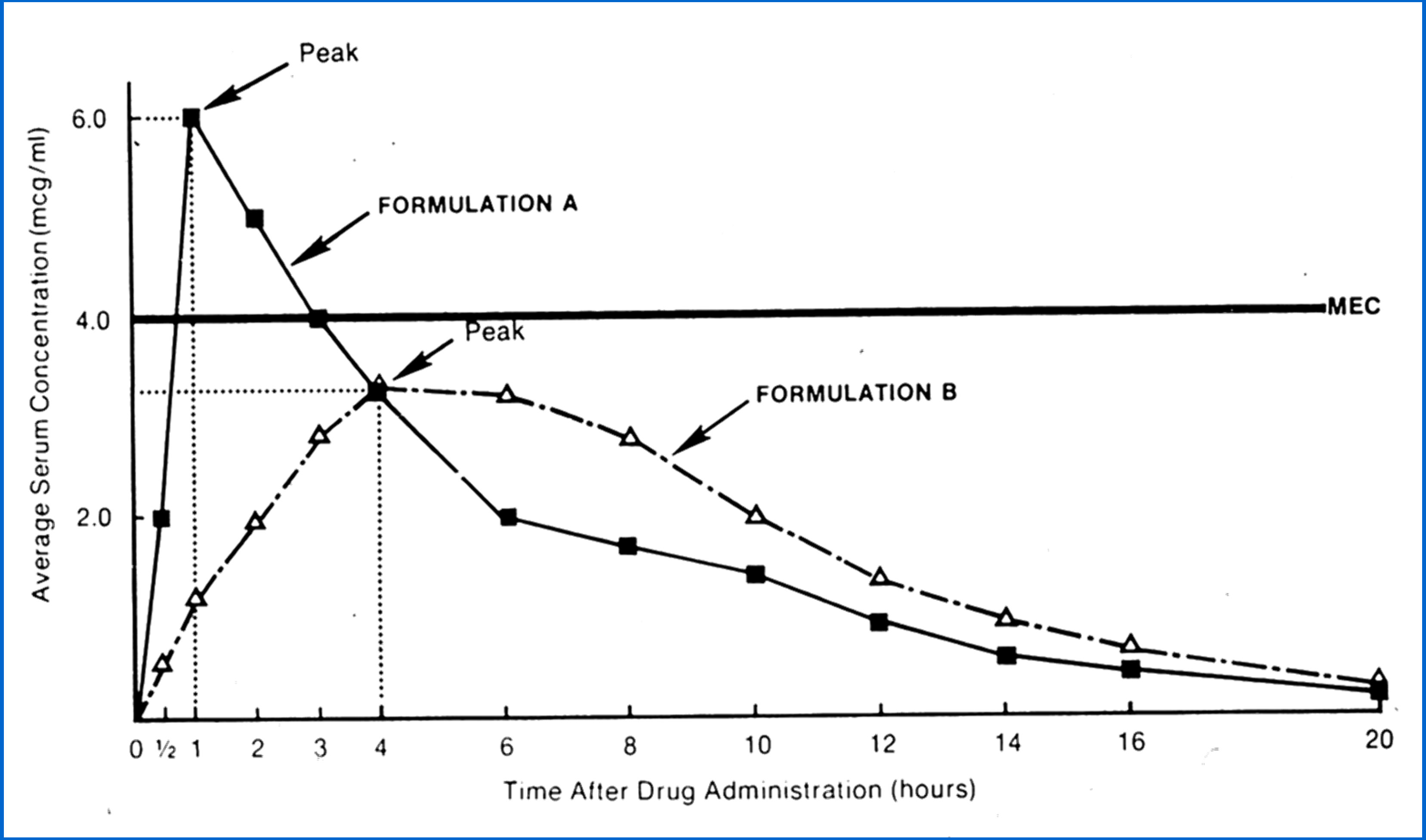
AUC A > B:
B INEFFECTIVE



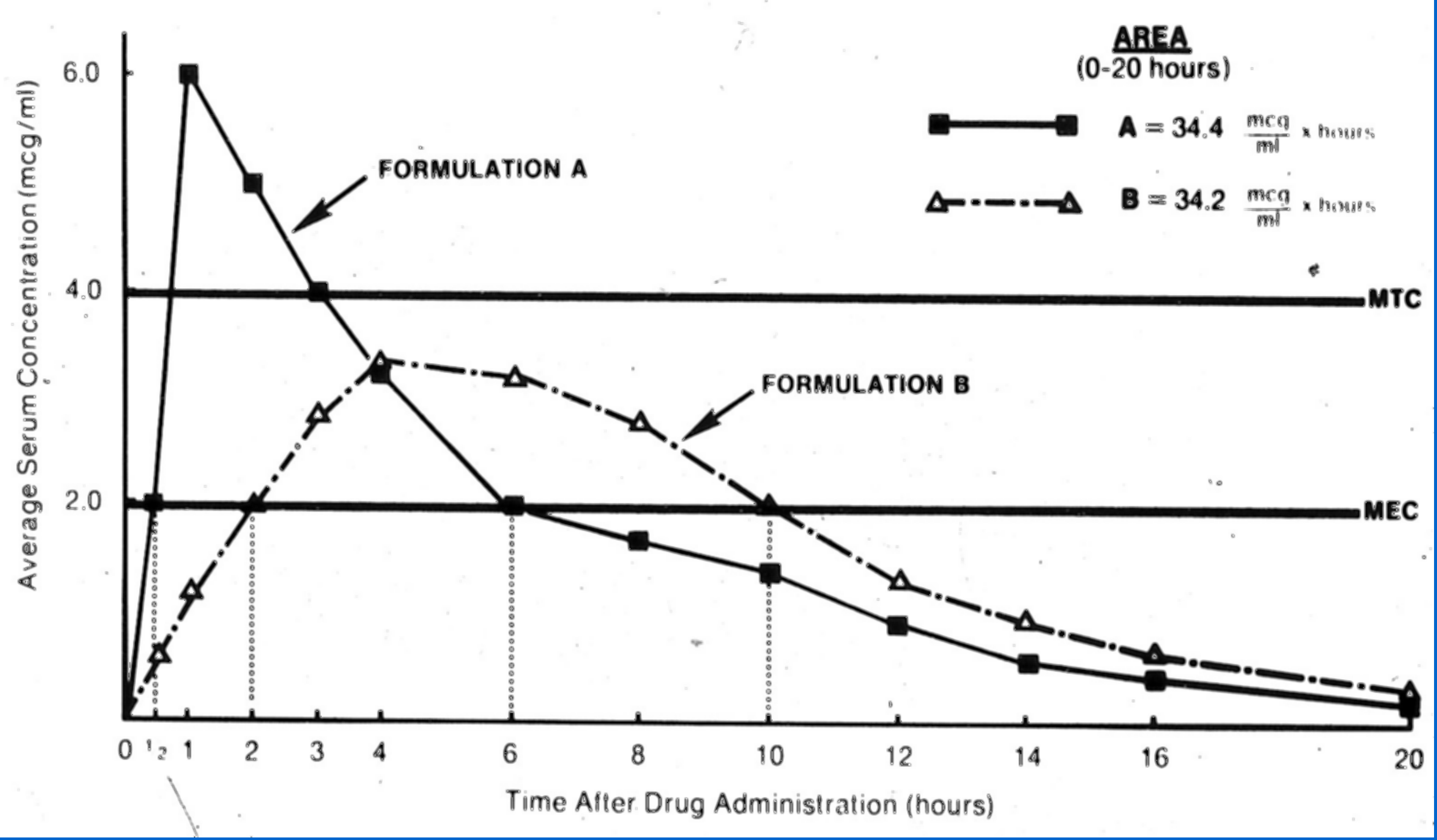
AUC A > B: A AND B EQUALLY EFFECTIVE



EQUAL AUC BUT DIFFERENT k_a: B IS INEFFECTIVE



EQUAL AUC BUT DIFFERENT k_a: A IS TOXIC



RELATIVE BIOAVAILABILITY CONCLUSIONS

- BIOEQUIVALENCE =

  THERAPEUTIC EQUIVALENCE

- BIOINEQUIVALENCE NOT NECESSARILY =

  THERAPEUTIC INEQUIVALENCE

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WHY DRUG DEVELOPMENT FAILS*

- UNSUITABLE BIOPHARMACEUTICAL PROPERTIES
- UNSUITABLE CLINICAL PK
- PHARMACOLOGY DOESN'T WORK IN HUMANS
- UNEXPECTED TOXICITY IS ENCOUNTERED

* Ronald E. White, Bristol-Myers Squibb (From Good Ligands to Good Drugs, AAPS-NIGMS Symposium, February 19-21, 1998)

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS I:

HIGH SOLUBILITY-HIGH PERMEABILITY

CLASS II:

LOW SOLUBILITY-HIGH PERMEABILITY

CLASS III:

HIGH SOLUBILITY-LOW PERMEABILITY

CLASS IV:

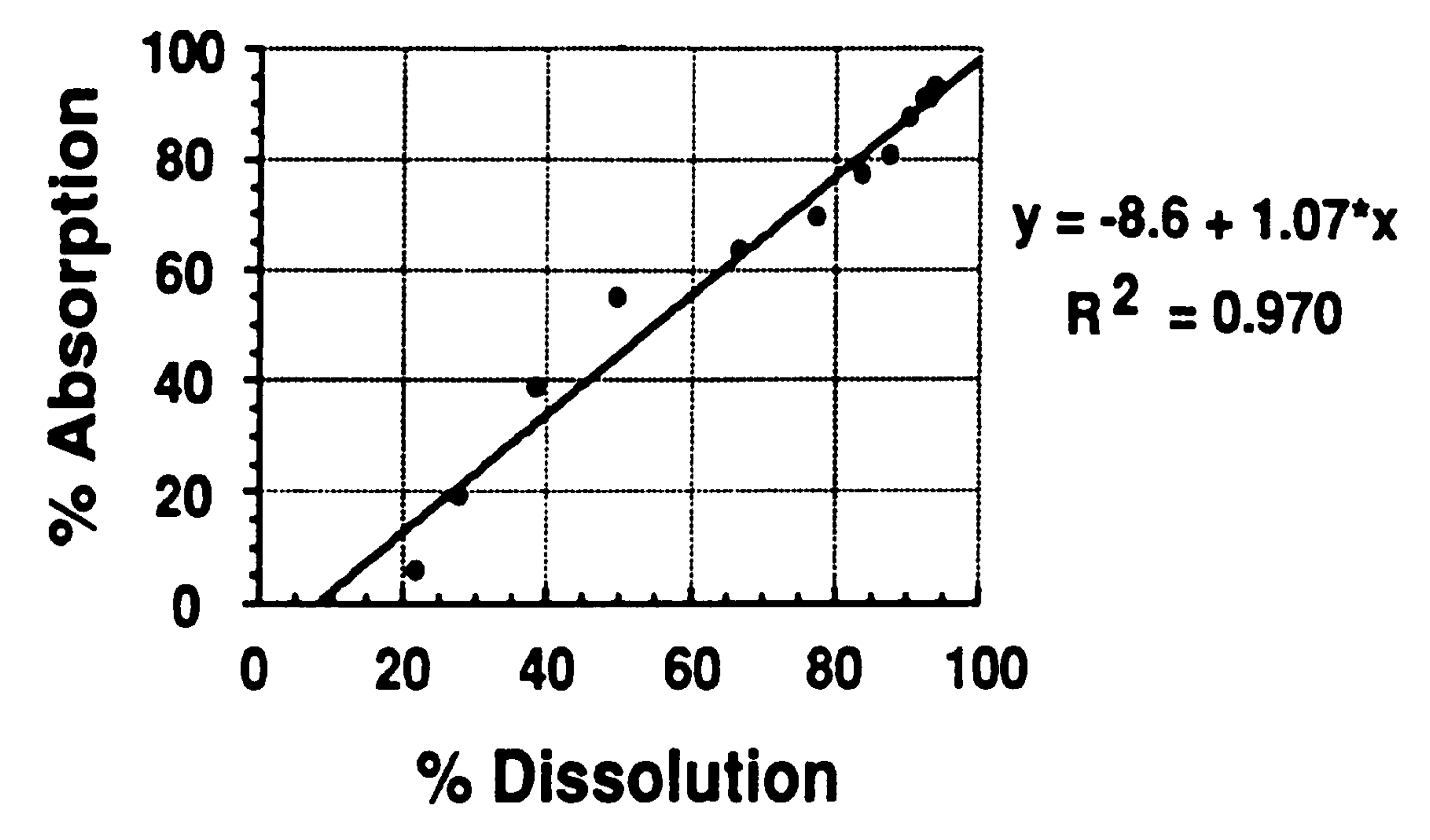
LOW SOLUBILITY-LOW PERMEABILITY

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

THREE CRITICAL BIOPHARMACEUTICAL PROPERTIES

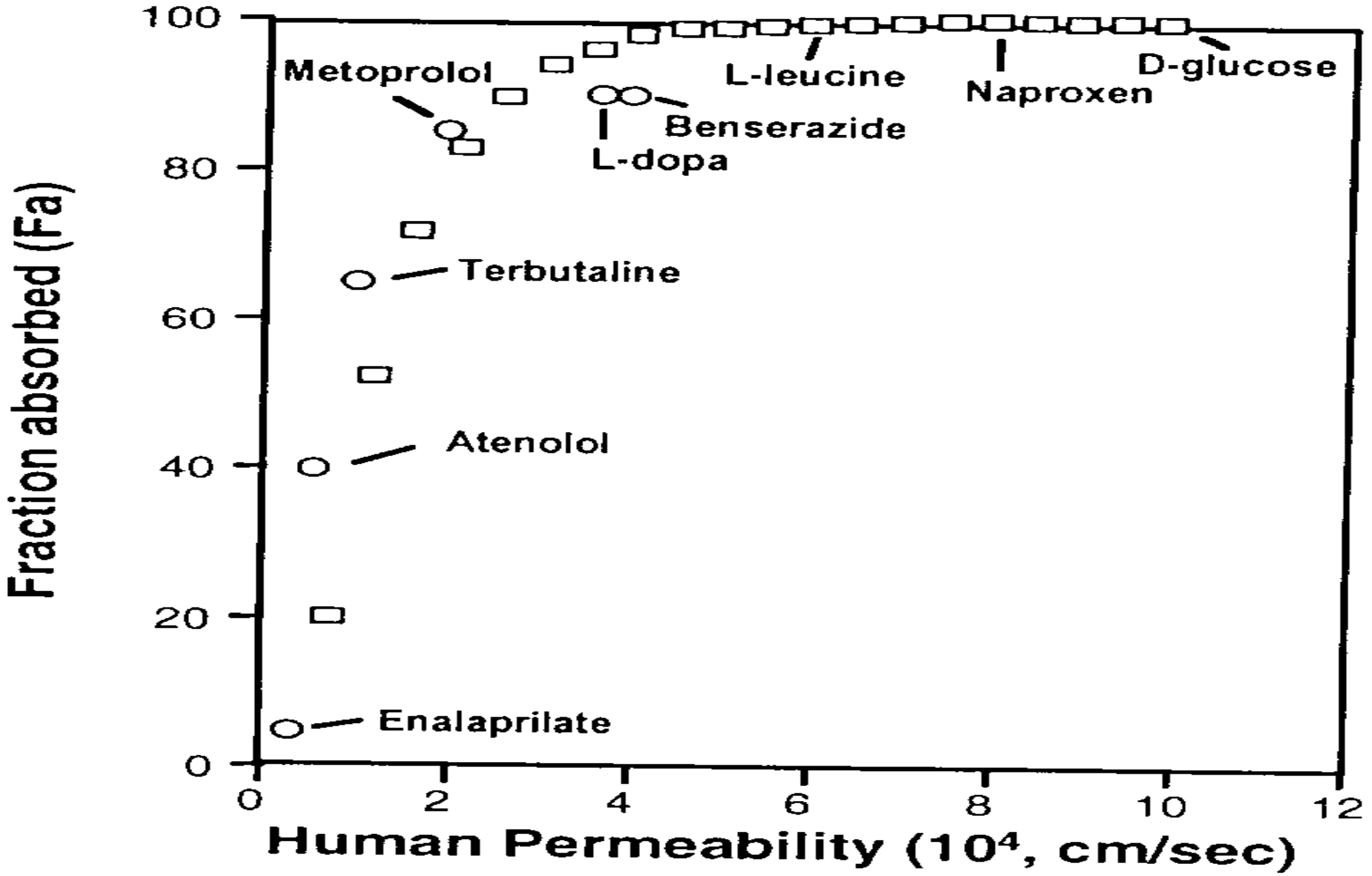
- **DRUG SOLUBILITY RELATIVE TO DOSE**
- **DISSOLUTION RATE OF FORMULATION**
- **INTESTINAL PERMEABILITY OF DRUG**

CORRELATION OF RATES OF DRUG DISSOLUTION AND ORAL ABSORPTION



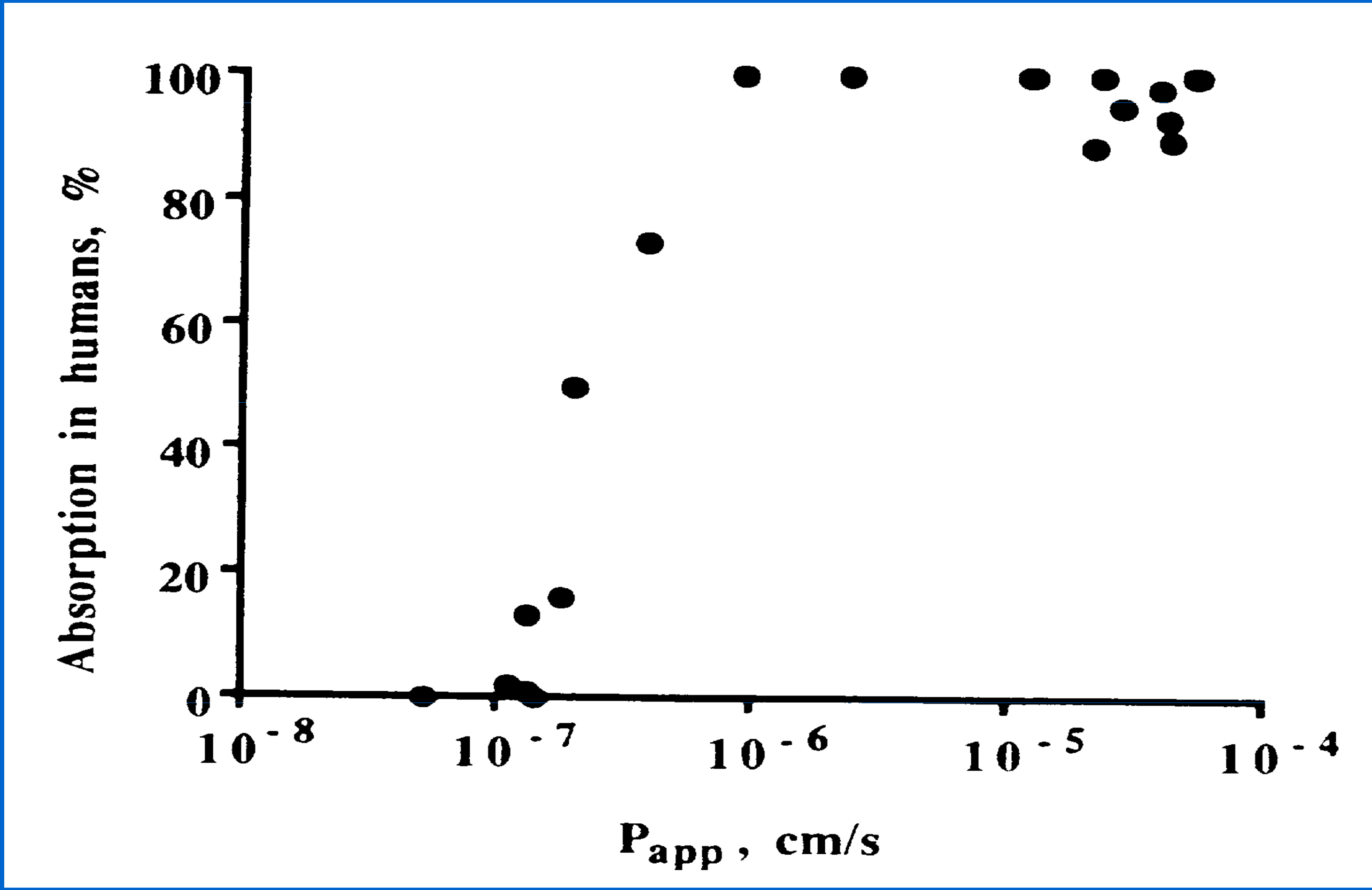
* From Rackley RJ. In Young D, Devane JG, Butler J, eds. In vitro-in vivo correlations. p. 1-15.

BIOAVAILABILITY VS. JEJEUNAL PERMEABILITY *



* From Amidon GL et al. Pharm Res 1995;12:413-20.

BIOAVAILABILITY VS. Caco-2 CELL PERMEABILITY P_{app}*



* From Arturson P, Karlsson J. Biochem Biophys Res Commun 1991; 175:880-5.

DEFICIENCIES OF Caco-2 CELL MODEL

- ↓ PARACELLULAR PERMEABILITY
- ↓ DRUG METABOLIZING ENZYMES & TRANSPORTERS
- NO HEPATIC FIRST-PASS METABOLISM

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS I:

HIGH SOLUBILITY-HIGH PERMEABILITY

- ***in vitro – in vivo*** **correlation generally good**
- ***but*** **no way to account for 1st pass metabolism**

*** From: Amidon GL, et al. Pharm Res 1995;12:413-20**

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS II:

LOW SOLUBILITY-HIGH PERMEABILITY

- rate of absorption limited by dissolution rate
- *in vitro – in vivo* correlation tenuous since many factors may affect dissolution

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS III:

HIGH SOLUBILITY-LOW PERMEABILITY

- **Intestinal reserve length is marginal.**
- **If dissolution is rapid, bioavailability will reflect intestinal permeability and transit time.**

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS IV:

LOW SOLUBILITY-LOW PERMEABILITY

- *in vitro – in vivo* correlation poor
- good bioavailability not expected

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

THE BOTTOM LINE

CLASS I DRUGS:

HIGH SOLUBILITY-HIGH PERMEABILITY

- **Preferred as development candidates**
- **FDA may waive repeat *in vivo* testing if initial formulation has good bioavailability*.**

*** Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, CDER Guidance for Industry, August 2000.**